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(54) N-(3-benzofuranyl)urea-derivatives

N-(3-Benzofuranyl)Harnstoffderivate
Dérivés de N-(3-benzofuranyl)urée

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EP-A- 0 069 521 **EP-A- 0 146 243**

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Description

[0001] The invention relates to N-(3-benzofuranyl)urea-derivatives, processes for their preparation and their use in medicaments.

[0002] It is known that the NADPH oxidase of phagocytes is the physiological source to the superoxide radical anion and reactive oxygen species derived therefrom which are important in the defence against pathogens. Moreover, both inflammatory (e.g. TNF α , IL-1 or IL-6) and anti-inflammatory cytokines (e.g. IL-10) play a pivotal role in host defence mechanism. Uncontrolled production of inflammatory mediators can lead to acute or chronic inflammation, auto immune diseases, tissue damage, multi-organ failure and to death. It is additionally known that elevation of phagocyte cyclic AMP leads to inhibition of oxygen radical production and that this cell function is more sensitive than others such as aggregation or enzyme release.

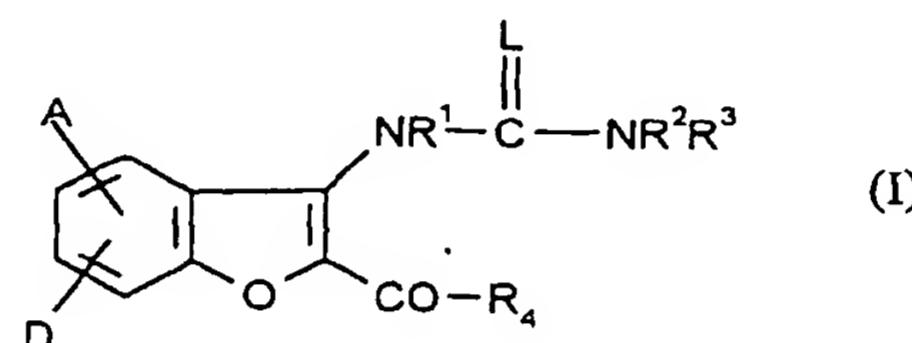
[0003] Benzofuran- and benzothiophene derivatives having lipoxygenase-inhibiting action are described in the publication EP 146 243.

[0004] The invention relates to N-(3-benzofuranyl)urea-derivatives of the general formula (I)

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in which

A and D are identical or different and represent hydrogen, straight-chain or branched acyl or alkoxy carbonyl, each having up to 6 carbon atoms, or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by carboxyl or alkoxy carbonyl having up to 6 carbon atoms, phenoxy or benzoyl, or represent halogen, carboxyl, cyano, nitro, trifluoromethyl, trifluoromethoxy or a group of a formula -OR⁵, -S(O)_aR⁶, -(O-CH₂-CO)_b-NR⁷R⁸, -CO-NR⁹R¹⁰, -SO₂-NR¹¹R¹² or -NH-SO₂R¹³, in which

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R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹ and R¹²

are identical or different and denote hydrogen, cycloalkyl having 3 to 6 carbon atoms, benzyl or a 5 to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the series comprising N, S and O and to which a phenyl ring can be fused and which is optionally substituted by identical or different substituents from the series comprising halogen, cyano, nitro or by a straight-chain or branched alkyl having up to 6 carbon atoms or
denote straight-chain or branched alkyl, alkenyl or acyl each having up to 8 carbon atoms, or
denote phenyl, which is optionally monosubstituted to disubstituted by identical or different substituents from the series comprising nitro, halogen, carboxy or straight-chain or branched alkoxy carbonyl having up to 6 carbon atoms,

or

R⁵ denotes a hydroxyl protecting group or straight-chain or branched alkoxy carbonyl having up to 6 carbon atoms, or
denotes straight-chain or branched alkyl having up to 8 carbon atoms, which is substituted by carboxyl, hydroxyl, straight-chain or branched acyl or alkoxy carbonyl each having up to 6 carbon atoms, phenoxy, benzoyl or by a 5 to 7-membered unsaturated heterocycle having up to 3 hetero atoms from the series comprising N, S and/or O, which is optionally substituted by halogen, cyano, nitro

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or by straight-chain or branched alkyl having up to 6 carbon atoms

or

5 R⁵ denotes a group of a formula SO₂R¹⁴,
in which
R¹⁴ denotes phenyl, trifluormethyl or straight-chain or branched alkyl having up to 4 carbon atoms,

10 a denotes a number 0, 1 or 2,
b denotes a number 0 or 1,
R⁷ denotes hydrogen or a straight-chain or branched alkyl having up to 4 carbon atoms,
R¹³ denotes aryl having up 6 to 10 carbon atoms, trifluoromethyl or straight-chain or branched alkyl having up to 6 carbon atoms,

15 R¹ represents hydrogen, straight-chain or branched alkyl having up to 6 carbon atoms, an aminoprotecting group or a group of the formula -CO-R¹⁵,
in which

20 R¹⁵ denotes hydroxyl, straight chain or branched alkoxy carbonyl having up to 6 carbon atoms, cycloalkyl having up 3 to 6 carbon atoms, pyridyl, pyrrolidinyl or straight chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by halogen, carboxyl or straight chain or branched alkoxy carbonyl having up to 6 carbon atoms, or
25 denotes phenyl, which is optionally substituted by hydroxyl, carboxyl or straight chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,

L represents an oxygen or sulfur atom,
R² and R³ are identical or different and represent hydrogen, cycloalkyl having up to 6 carbon atoms, straight chain or branched alkyl, alkoxy carbonyl or alkenyl each having up to 8 carbon atoms, or represent benzoyl or aryl having 6 to 10 carbon atoms, which are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising halogen, cyano, nitro, carboxyl, straight-chain or branched alkyl, alkoxy, alkoxy carbonyl or acyl each having up to 6 carbon atoms,

30 or
35 R² and R³ together with the nitrogen atom form a 5- to 7-membered saturated heterocycle optionally having a further O atom,

and
40 R⁴ represents phenyl, which is optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, thiophenyl, cycloalkyl having up to 3 to 6 carbon atoms, halogen, nitro, tetrazolyl, thiazolyl, furanyl, pyridyl, trifluoromethyl, difluoromethyl, cyano, carboxyl, straight-chain or branched alkyl, alkoxy, alkoxy carbonyl or acyl each having up to 8 carbon atoms, or
45 phenyl is optionally substituted by phenyl, which is optionally monosubstituted to disubstituted by halogen, or by a group of a formula -NR¹⁶R¹⁷, -SR¹⁸, SO₂R¹⁹ or -O-SO₂R²⁰,
in which

50 R¹⁶ and R¹⁷ have the abovementioned meaning of R⁷ and R⁸ and are identical or different to the latter,
or
55 R¹⁶ denotes hydrogen,
and
R¹⁷ denotes straight-chain or branched acyl having up to 6 carbon atoms,

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R¹⁸ denotes hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,
R¹⁹ and R²⁰ are identical or different and represent straight-chain or branched alkyl having up to 6 carbon atoms, benzyl or phenyl,

5 and salts thereof.

[0005] The N-(3-benzofuranyl)urea-derivatives according to the invention can also be present in the form of their salts. In general, salts with organic or inorganic bases or acids may be mentioned here.

[0006] Physiologically acceptable salts are preferred in the context of the present invention. Physiologically acceptable salts of the N-(3-benzofuranyl)urea-derivatives can be metal or ammonium salts of the substances according to the invention, which contain a free carboxylic group. Those which are particularly preferred are, for example, sodium, potassium, magnesium or calcium salts, and also ammonium salts which are derived from ammonia, or organic amines, such as, for example, ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine or ethylenediamine.

[0007] Physiologically acceptable salts can also be salts of the compounds according to the invention with inorganic or organic acids. Preferred salts here are those with inorganic acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or salts with organic carboxylic or sulphonic acids such as, for example, acetic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, ethanesulphonic acid, benzenesulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid.

[0008] The compounds according to the invention can exist in stereoisomeric forms which either behave as image and mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the antipodes and to the racemate forms, as well as the diastereomer mixtures. The racemate forms, like the diastereomers, can be separated into the stereoisomerically uniform constituents in a known manner.

[0009] Heterocycle in general represents a 5- to 7-membered saturated or unsaturated, preferably 5- to 6-membered, saturated or unsaturated ring which can contain up to 3 oxygen, sulphur and/or nitrogen atoms as heteroatoms and to which further aromatic ring can be fused.

[0010] The following are mentioned as preferred: thienyl, furyl, pyrrolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxazolyl, cinnolyl, thiazolyl, dihydrothiazolyl, benzothiaazolyl, iso-thiazolyl, benzothiazolyl, oxazolyl, benzoxazolyl, isoxazolyl, imidazolyl, benzimidazolyl, indolyl, morpholinyl, pyrrolidinyl, piperidyl, piperazinyl, oxazolyl, oxazolinyl or triazolyl.

[0011] Amino protective group in the context of the above mentioned definition in general represents a protective group from the series comprising:

benzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert.butoxycarbonyl, allyloxycarbonyl, vinyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, cyclohexoxy carbonyl, 1,1-dimethylethoxycarbonyl, adamantly carbonyl, phthaloyl, 2,2,2-trichlorethoxycarbonyl, 2,2,2-trichlor-tert-butoxycarbonyl, menthoxycarbonyl, phenoxy carbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, formyl, acetyl, propionyl, pivaloyl, 2-chloracetyl, 2-bromacetyl, 2,2,2-trifluoracetyl, 2,2,2-trichloracetyl, benzoyl, 4-chlorbenzoyl, 4-brombenzoyl, 4-nitrobenzoyl, phthalimido, isovaleroyl oder benzyloxymethylene, 4-nitrobenzyl, 2,4-dinitrobenzyl or 4-nitrophenyl.

[0012] Preferred compounds of the general formula (I) are those in which

45 A and D are identical or different and represent hydrogen, straight-chain and branched acyl or alkoxy carbonyl each having up to 5 carbon atoms or straight-chain or branched alkyl having up to 4 carbon atoms which is optionally substituted by carboxyl, hydroxyl, alkoxy carbonyl having up to 5 carbon atoms, phenoxy or benzoyl, or represent fluorine, chlorine, bromine, nitro, trifluoromethyl or a group of a formula -OR⁵, -S(O)_a-R⁶, (O-CH₂-CO)_b-NR⁷R⁸, -CO-NR⁹R¹⁰, -SO-NR¹¹R¹² or -NH-SO₂-R¹³, in which

55 R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹ and R¹² are identical or different and denote hydrogen, cyclopropyl, cyclopentyl, cyclohexyl, chinolyl, pyridyl, imidazolyl, 1,3-thiazolyl or thienyl, which are optionally substi-

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tuted by identical or different substituents from the series comprising fluorine, chlorine, bromine, iodine, cyano, nitro or by a straight-chain or branched alkyl having up to 5 carbon atoms,
denote straight-chain or branched alkyl, alkenyl or acyl each having up to 6 carbon atoms, or
denote phenyl, which is optionally monosubstituted to disubstituted by identical or different substituents from the series comprising nitro, fluorine, chlorine, bromine, iodine, carboxyl or straight-chain or branched alkoxy carbonyl having up to 5 carbon atoms,

or

R⁵ denotes benzyl, acetyl or tetrahydropyranyl or straight chain or branched alkoxy carbonyl having up to 4 carbon atoms,
denotes straight-chain or branched alkyl having up to 6 carbon atoms, which is substituted by carboxyl, hydroxyl, straight-chain or branched acyl or alkoxy carbonyl each having up to 4 carbon atoms, phenoxy, benzoyl or by pyridyl, imidazolyl, thienyl or furyl, which are optionally substituted by fluorine, chlorine, bromine, cyano, nitro or by straight-chain or branched alkyl having up to 4 carbon atoms,

or

R⁵ denotes a group of a formula -SO₂-R¹⁴,
in which

R¹⁴ denotes phenyl, trifluormethyl or straight-chain or branched alkyl having up to 3 carbon atoms,

a denotes a number 0, 1 or 2,

b denotes a number 0 or 1,

R⁷ denotes hydrogen or a straight-chain or branched alkyl having up to 3 carbon atoms,

R¹³ denotes phenyl, trifluormethyl or straight-chain or branched alkyl having up to 3 carbon atoms,

R¹ represents hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms, tert.butoxycarbonyl or a group of the formula -CO-R¹⁵
in which

R¹⁵ denotes hydroxyl, straight chain or branched alkoxy carbonyl having up to 4 carbon atoms, cyclopentyl, cyclohexyl, pyridyl, pyrrolidinyl or straight chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by fluorine, chlorine, bromine, carboxyl or straight chain or branched alkoxy carbonyl having up to 4 carbon atoms, or

denotes phenyl, which is optionally substituted by hydroxyl, carboxyl or straight chain or branched alkoxy or alkoxy carbonyl each having up to 4 carbon atoms,

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L represents an oxygen or sulfur atom,

R² and R³ are identical or different and represent hydrogen, cyclobutyl, cyclopentyl, cyclohexyl or straight-chain or branched alkyl, alkoxy carbonyl or alkenyl each having up to 6 carbon atoms, or
represent benzoyl or phenyl, which are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising fluorine, chlorine, bromine, iodine, carboxyl, cyano, nitro or by a straight-chain or branched alkyl, alkoxy or alkoxy carbonyl each having up to 5 carbon atoms,
or

R² and R³ together with the nitrogen atom form a pyrrolidinyl, piperidinyl or morpholinyl ring,
and

R⁴ represents phenyl, which is optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, thiophenyl, cyclopentyl, cyclohexyl, fluorine, chlorine, bromine, iodine, nitro, tetrazolyl, thiazolyl, furanyl, pyridyl, trifluoromethyl, difluoromethyl, cyano, carboxyl, straight-chain or branched alkyl, alkoxy, alkoxy carbonyl or acyl each having up to 6 carbon atoms, or
phenyl is optionally substituted by phenyl, which is optionally monosubstituted to disubstituted by fluorine, chlorine or bromine,
and salts thereof.

[0013] Particularly preferred compounds of the general formula (I) are those in which

A and D are identical or different and represent hydrogen, straight-chain or branched acyl or alkoxy carbonyl each having up to 4 carbon atoms, or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by carboxyl or alkoxy carbonyl having up to 4 carbon atoms, phenoxy or benzoyl, or represent
fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl, trifluoromethoxy, or a group of a formula -OR⁵, -S(O)_aR⁶, -(O-CH₂-CO)_b-NR⁷R⁸, -CO-NR⁹R¹⁰, -SO₂-NR¹¹R¹² or -NH-SO₂R¹³,
in which

R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹ and R¹² are identical and denote hydrogen, cyclopropyl, cyclopentyl, cyclohexyl, chinolyl, pyridyl, imidazolyl, 1,3-thiazolyl or thienyl, which are optionally substituted by identical or different substituents from the series comprising fluorine, chlorine, bromine, iodine, cyano, nitro or by a straight-chain or branched alkyl having up to 3 carbon atoms,
denote straight-chain or branched alkyl, alkenyl or acyl each having up to 3 carbon atoms, or
denote phenyl, which is optionally monosubstituted to disubstituted by identical or different substituents from the series comprising nitro, fluorine, chlorine, bromine, iodine, carboxyl or straight-chain or branched alkoxy carbonyl having up to 3 carbon atoms,

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or

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R⁵ denotes benzyl, acetyl or tetrahydropyanyl or straight-chain or branched alkoxy carbonyl having up to 3 carbon atoms, denotes straight-chain or branched alkyl having up to 4 carbon atoms, which is substituted by carboxyl, hydroxyl, straight-chain or branched acyl or alkoxy carbonyl each having up to 3 carbon atoms, phenoxy, benzoyl or by pyridyl, imidazolyl or thienyl,

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or

R⁵ denotes a group of a formula -SO₂-R¹⁴, in which

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R¹⁴ denotes phenyl, trifluormethyl or methyl,

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a denotes a number 0, 1 or 2,

b denotes a number 0 or 1,

R⁷ denotes hydrogen, methyl or ethyl,

R¹³ denotes phenyl, trifluoromethyl or methyl,

25

R¹ represents hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms or a group of the formula -CO-R¹⁵, in which

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R¹⁵ denotes hydroxyl, straight chain or branched alkoxy carbonyl having up to 3 carbon atoms, cyclopentyl, cyclohexyl, pyridyl, pyrrolidinyl or straight chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by fluorine, chlorine, bromine, carboxyl or straight chain or branched alkoxy carbonyl having up to 3 carbon atoms, or

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denotes phenyl, which is optionally substituted by hydroxyl, carboxyl or straight chain or branched alkoxy or alkoxy carbonyl each having up to 3 carbon atoms,

L represents an oxygen or sulfur atom,

40

R² and R³ are identical or different and represent hydrogen, cyclobutyl, cyclopentyl, cyclohexyl or straight-chain or branched alkyl, alkoxy carbonyl or alkenyl each having up to 5 carbon atoms, or represent benzoyl or phenyl, which are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising fluorine, chlorine, bromine, iodine, carboxy, cyano, nitro or by a straight-chain or branched alkyl, alkoxy or alkoxy carbonyl each having up to 3 carbon atoms,

or

45 R² and R³ together with the nitrogen atom form a pyrrolidinyl ring,

and

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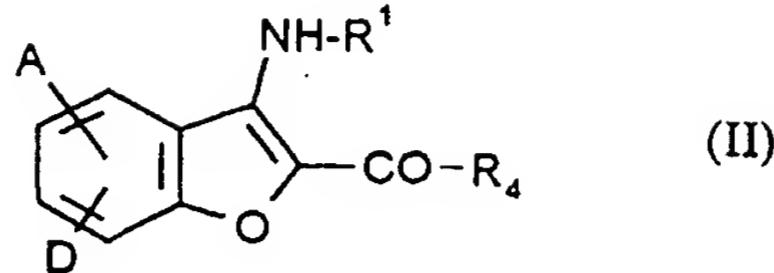
R⁴ represents phenyl, which is optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, thiophenyl, cyclopentyl, cyclohexyl, fluorine, chlorine, bromine, nitro, tetrazolyl, thiazolyl, furanyl, pyridyl, trifluoromethyl, difluoromethyl, cyano, carboxyl, straight-chain or branched alkyl, alkoxy, alkoxy carbonyl or acyl each having up to 5 carbon atoms, or phenyl is optionally substituted by phenyl, which is optionally monosubstituted to disubstituted by chlorine,

and salts thereof.

55 [0014] A process for the preparation of the compounds of the general formula (I) has additionally been found, characterized in that compounds of the general formula (II)

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in which

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A, D, R¹ and R⁴ have the abovementioned meaning
are reacted with compounds of the general formula (III)

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in which

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L and R² have the abovementioned meaning,

in inert solvents, if appropriate in the presence of a base and/or in the presence of an auxiliary,
and in the case of R²/R³ = H and L = O,
compounds of the general formula (II) are reacted with compounds of the general formula (IIIa)

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in which

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E denotes halogen, preferably chlorine,

and in the case of R²/R³ = H and L = S,
compounds of the general formula (II) are reacted with NH₄SCN,

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and in case of R¹, R² and/or R³ ≠ H the amino groups are derivated optionally by common methods.

[0015] The process according to the invention can be illustrated by way of example by the following equations:

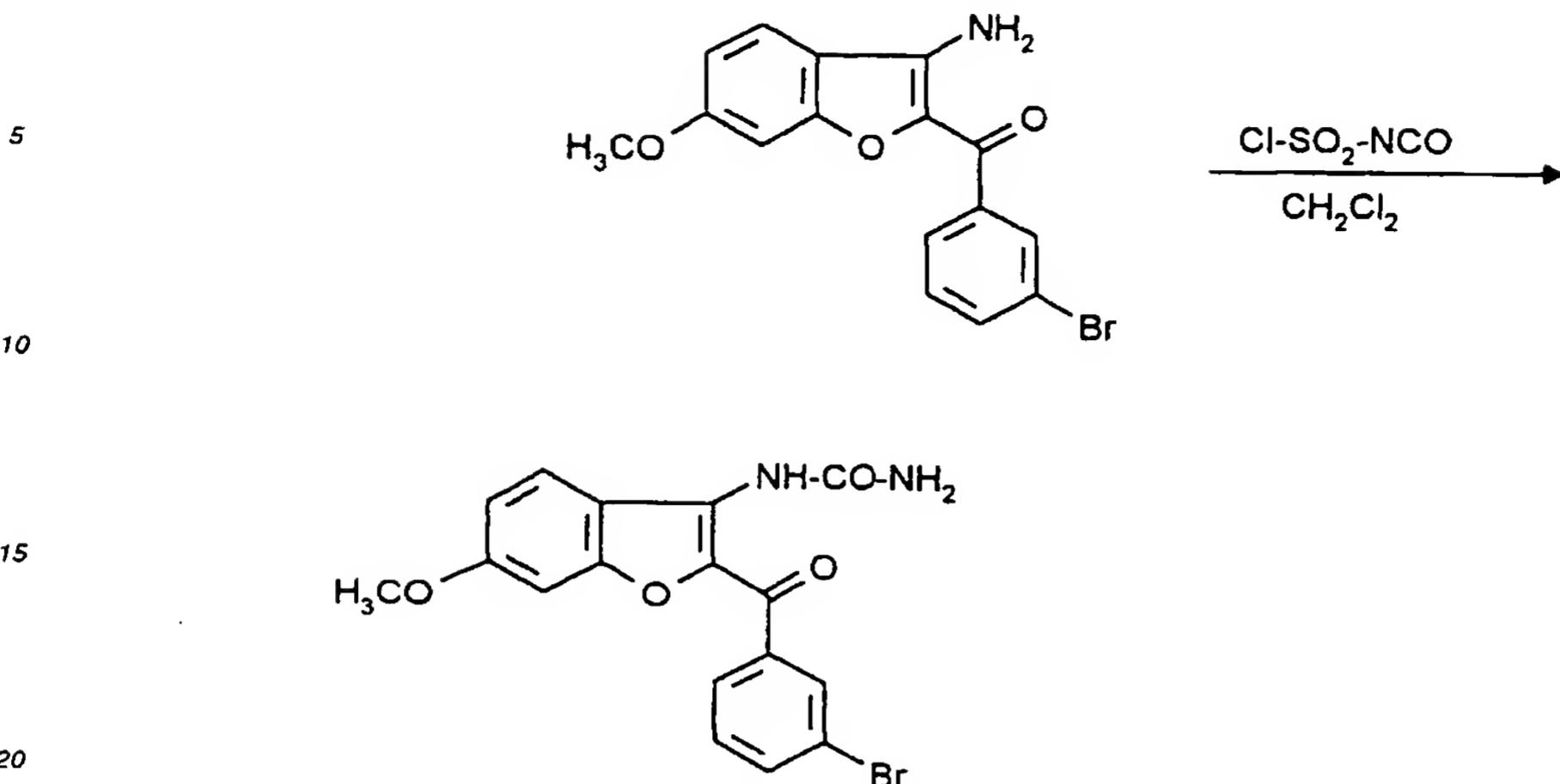
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[0016] Suitable solvents are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, dioxane or tetrahydrofuran, acetone, dimethylsulfoxide, dimethylformamide or alcohols such as methanol, ethanol, propanol or halogenohydrocarbons such as dichlormethane, trichloromethane or tetrachloromethane. Dichloromethane is preferred.

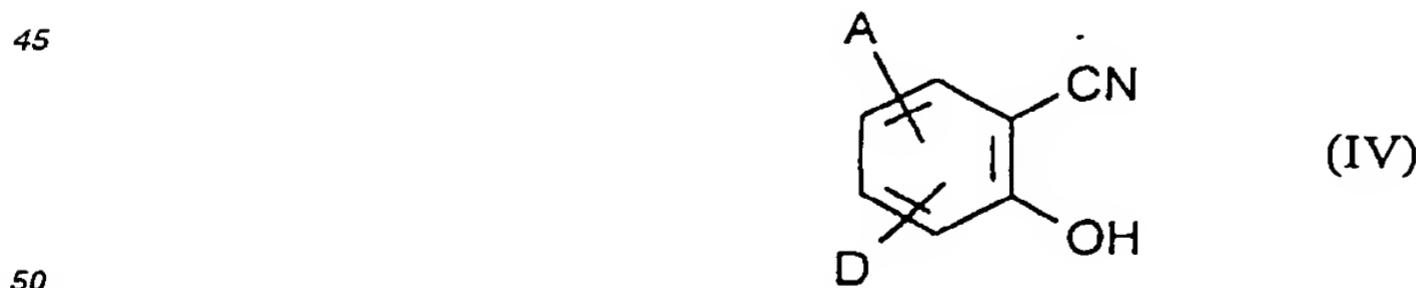
[0017] Suitable bases are generally inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, sodium hydroxide, sodium hydrogencarbonate or potassium hydroxide, alkaline earth metal hydroxides such as, for example, barium hydroxide, alkali metal carbonates such as sodium carbonate, potassium carbonate, alkaline earth metal carbonates such as calcium carbonate, or alkaline metal or organic amines (trialkyl (C₁-C₆)amines) such as triethylamine, or heterocycles such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabi-cyclo[5.4.0]undec-7-ene (DBU), or amides such as sodium amides, lithium butyl amide or butyllithium, pyridine or methylpiperidine. It is also possible to employ alkali metals, such as sodium or its hydrides such as sodium hydride, as bases. Potassium carbonate, triethylamine, sodium hydrogencarbonate and sodium-hydroxide are preferred.

[0018] The process is in general carried out in a temperature range from -30°C to +100°C, preferably from -10°C to +50°C.

[0019] The process is generally carried out at normal pressure. However, it is also possible to carry out it at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

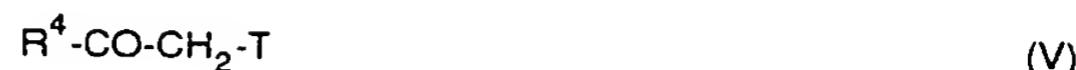
[0020] The base is employed in an amount from 1 mol to 10 mol, preferably from 1.0 mol to 4 mol, relative to 1 mol of the compounds of the general formulae (III) or (IIIa).

[0021] The compounds of the general formula (II) are as species new and are prepared by first reacting compounds of the general formula (IV)



in which

A and D have the abovementioned meaning
55 with compounds of the general formula (V)



in which

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R^4 has the abovementioned meaning

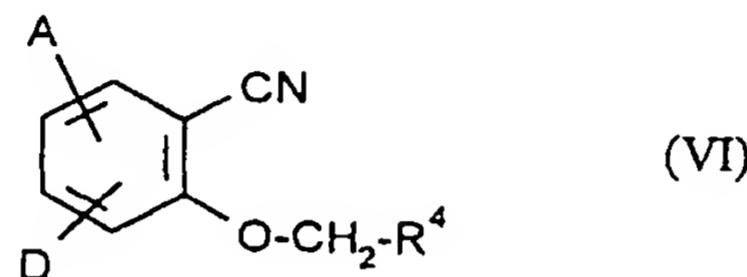
and

10 T represents a typical leaving group such as, for example, chlorine, bromine, iodine, tosylate or mesylate, preferably bromine,

to prepare compounds of the general formula (VI)

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in which

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A, D and R^4 have the abovementioned meaning,
in one of the abovementioned solvents and bases, preferably triethylamine and dimethylformamide,
which in a further last step are reacted with $\text{NaOC}_2\text{H}_5/\text{C}_2\text{H}_5\text{OH}$.

30 [0022] The process is in general carried out in a temperature range from +10°C to +150°C, preferably from +30°C to +80°C.

[0023] The process is generally carried out at normal pressure. However, it is also possible to carry out it at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

35 [0024] The compounds of the general formulae (III), (IIIa), (IV), (V) and (VI) are known and in some cases new and can be prepared by customary methods.

[0025] Surprisingly it was found that compounds given by the general formula (I) inhibited oxygen radical formation as well as TNF α (tumor necrosis factor) production, but potentiated the release of IL-10. These compounds elevated cellular cyclic AMP probably by inhibition of phagocyte phosphodiesterase activity.

40 [0026] The compounds according to the invention specifically inhibit the production of superoxide by polymorphonuclear leukocytes (PMN). Furthermore, these compounds inhibit TNF α release and potentiate IL-10 production in human monocytes in response to a variety of stimuli including bacterial lipopolysaccharide (LPS), complement-opsonized zymosan (ZymC3b) and IL-1 β .

[0027] The described effects are probably mediated by the elevation of cellular cAMP probably due to inhibition of the type IV phosphodiesterase responsible for its degradation.

45 [0028] They can therefore be employed in medicaments for the treatment of acute and chronic inflammatory processes.

[0029] The compounds according to the invention are preferably suitable for the treatment and prevention of acute and chronic inflammation and auto immune diseases, such as emphysema, alveolitis, shock lung, all kinds of asthma, COPD, ARDS, bronchitis, arteriosclerosis, arthrosis, inflammations of the gastro-intestinal tract, rheumatoide arthritis, myocarditis, sepsis and septic shock, arthritis, rheumatoid spondylitis and osteoarthritis, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, bone resorption diseases, reperfusion injury, graft vs host reaction, allograft rejection malaria, myalgias, HIV, AIDS, cachexia, Crohn's disease, ulcerative colitis, pyresis, system lupus erythematosus, multiple sclerosis, type I diabetes mellitus, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease and leukemia. The compounds according to the invention are additionally suitable for reducing the damage to infarct tissue after reoxygenation. In this case the simultaneous administration of allopurinol to inhibit xanthine oxidase is of advantage. Combination therapy with superoxide dismutase is also of use.

Test description

[0030]

5 1. Preparation of human PMN

Blood was taken from healthy subjects by venous puncture and neutrophils were purified by dextran sedimentation and resuspended in the buffered medium.

10 2. Inhibition of FMLP-stimulated production of superoxide radical anions. Neutrophils ($2.5 \times 10^5 \text{ ml}^{-1}$) were mixed with cytochrome C (1.2 mg/ml) in the wells of a microtitre plate. Compounds according to the invention were added in dimethyl sulphoxide (DMSO). Compound concentration ranged from 2.5 nM to 10 μM , the DMSO concentration was 0.1% v/v in all wells. After addition of cytochalasin b (5 $\mu\text{g} \times \text{ml}^{-1}$) the plate was incubated for 5 min at 37°C. Neutrophils were then stimulated by addition of $4 \times 10^{-8} \text{ M}$ FMLP and superoxide generation measured as superoxide dismutase inhibitable reduction of cytochrome C by monitoring the OD_{550} in a Thermomax microtitre plate spectrophotometer. Initial rates were calculated using a Softmax kinetic calculation programme. Blank wells contained 200 units of superoxide dismutase.

The inhibition of superoxide production was calculated as follows:

$$20 \quad \frac{[1 - ((Rx - Rb))]}{((Ro - Rb))} \cdot 100$$

Rx = Rate of the well containing the compound according to the invention.

Ro = Rate in the control well.

Rb = Rate in the superoxide dismutase containing blank well.

25 Compounds according to the invention have IC_{50} values in the range 0,07 μM -10 μM .

30 3. Measurement of PMN cyclic AMP concentration

The compounds according to the invention were incubated with $3.7 \times 10^6 \text{ PMN}$ for 5 min at 37°C before addition of $4 \times 10^{-8} \text{ M}$ FMLP. After 6 min protein was precipitated by the addition of 1% v/v conc. HCl in 96% v/v ethanol containing 0.1 mM EDTA. After centrifugation the ethanolic extracts were evaporated to dryness under N_2 and resuspended in 50 mM Tris/HCl pH 7.4 containing 4 mM EDTA. The cyclic AMP concentration in the extracts was determined using a cyclic AMP binding protein assay supplied by Amersham International plc. Cyclic AMP concentrations were expressed as percentage of vehicle containing control incubations.

35 Compounds elevate the cAMP-level at 1 μM compound 0-400% of control values.

40 4. Assay of PMN phosphodiesterase

This was performed as a particulate fraction from human PMN essentially as described by Souness and Scott (Biochem. J. 291, 389-395, 1993). Particulate fractions were treated with sodium vanadate / glutathione as described by the authors to express the discrete stereospecific site on the phosphodiesterase enzyme. Compounds according to the invention had IC_{50} values ranging from 0,001 μM to 10 μM .

45 5. Assay of human platelet phosphodiesterase

This was performed essentially as described by Schmidt et al (Biochem. Pharmacol. 42, 153-162, 1991) except that the homogenate was treated with vanadate glutathione as above. Compounds according to the invention had IC_{50} values greater than 100 μM .

50 6. Assay of binding to the rolipram binding site in rat brain membranes This was performed essentially as described by Schneider et al. (Eur. J. Pharmacol. 127, 105-115, 1986). Compounds according to the invention had IC_{50} values in the range 0,01 to 10 μM .

55 7. Preparation of human monocytes

Blood was taken from normal donors. Monocytes were isolated from peripheral blood by density centrifugation, followed by centrifugal elutriation.

8. Endotoxin induced TNF release

Monocytes ($1 \times 10^6 \text{ ml}^{-1}$) were stimulated with LPS (2 $\mu\text{g} \text{ ml}^{-1}$) and coincubated with the compounds at different concentrations (10^{-4} to 10 $\mu\text{g} \text{ ml}^{-1}$). Compounds were dissolved in DMSO/medium (2% v/v). The cells were incu-

EP 0 731 099 B1

bated in RPMI-1640 medium glutamine/FCS supplemented and at 37°C in a humidified atmosphere with 5% CO₂. After 18 to 24 hours TNF was determined in the supernatants by an human TNF specific ELISA (medgenix). Controls were nonstimulated and LPS stimulated monocytes without compounds. Example 2, 13 and 16 induce inhibition of LPS driven TNF activity in human monocytes (IC₅₀: 10⁻³ to 1 µg ml⁻¹).

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9. Endotoxin induced shock lethality in mice

B6D2F1 mice (n=10) were sensitized with galactosamine (600 mg/kg), and shock and lethality were triggered by LPS (0.01 µg/mouse). The compounds were administered intravenously 1 hour prior LPS. Controls were LPS challenged mice without compound. Mice were dying 8 to 24 hours post LPS challenge. Example 2, 13 and 16 reduced the endotoxin mediated mortality about 70% to 100% at doses of 3 to 30 mg/kg.

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The galactosamine / LPS mediated mortality was reduced.

15 10. Stimulation of human monocytes and determination of cytokine levels Human monocytes (2x10⁵ in 1 ml) were stimulated with 100 ng/ml LPS, 0.8 mg/ml zymC3b or 10 ng/ml IL-1β in the presence of test compounds. The final DMSO concentration was maintained at 0.1 % v/v. Cells were incubated overnight in a humidified atmosphere of 5% CO₂ at 37°C. Supernatants were harvested and stored at -70°C. The TNFα concentration was measured by ELISA using the A6 anti-TNF monoclonal antibody (Miles) as the primary antibody. The secondary antibody was the polyclonal anti-TNFα antibody IP300 (Genzyme) and the detection antibody was a polyclonal anti-rabbit IgG alkaline phosphatase conjugate (Sigma). IL-10 was determined by ELISA (Biosource). Example 2 inhibits the LPS- and IL-1β-induced TNFα production with an IC₅₀ of 1-2 µM, while the zymC3b-induced TNFα production was inhibited by approximately 50% at 10 µM. Example 2 also potentiates the release of IL-10, without stimulating IL-10 production by itself. There is approximately a 3-4 fold increase in IL-10 production at 10 µM.

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[0031] The new active compounds can be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert, nontoxic, pharmaceutically suitable excipients or solvents. In this connection, the therapeutically active compound should in each case be present in a concentration of about 0.5 to 90% by weight of the total mixture, i.e. in amounts which are sufficient in order to achieve the dosage range indicated.

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[0032] The formulations are prepared, for example, by extending the active compounds with solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, where, for example, in the case of the use of water as a diluent, organic solvents can be used as auxiliary solvents if appropriate.

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[0033] Administration is carried out in a customary manner, preferably orally or parenterally, in particular perlingually or intravenously.

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[0034] In the case of parenteral administration, solutions of the active compound can be employed using suitable liquid vehicles.

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[0035] In general, it has proved advantageous on intravenous administration to administer amounts from about 0.001 to 10 mg/kg, preferably about 0.01 to 5 mg/kg of body weight to achieve effective results, and on oral administration the dosage is about 0.01 to 25 mg/kg, preferably 0.1 to 10 mg/kg of body weight.

[0036] In spite of this, it may be necessary to depart from the amounts mentioned, in particular depending on the

body weight or the type of application route, on individual behaviour towards the medicament, the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be sufficient to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of administration of relatively large amounts, it is advisable to divide these into several individual doses over the course of the day.

Solvent

[0037]

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I	petrolether : ethylacetate 1:1
II	petrolether : ethylacetate 5:1
III	petrolether : ethylacetate 5:2
IV	ethylacetate
V	dichlormethane:methanol 5:1
VI	dichlormethane
VII	cyclohexane:ethylacetate 3:1

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(continued)

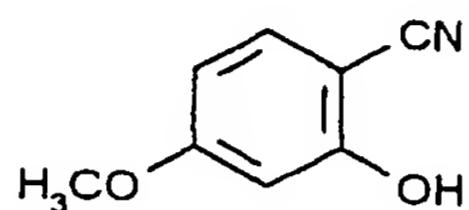
VIII	dichlormethane:methanol 50:1
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5 Starting compounds**Example I**

[0038] 2-Hydroxy-4-methoxybenzonitrile

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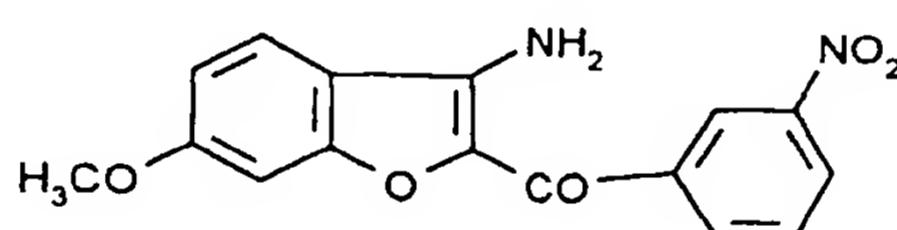
20 2-Hydroxy-4-methoxybenzaldehyde (55 g; 0.36 mol), hydroxylamine hydrochloride (30 g; 0.43 mol) and sodium formate (34 g; 0.5 mol) were refluxed in formic acid (200 ml; 98-100%) for 1.25 h. The solution was then rapidly chilled in an ice bath, with stirring over 30 min. The resulting precipitate was separated by filtration and washed well with water. Following drying, in a desicator under vacuum, the title compound was obtained (45 g; 0.3 mol; 84% yield) as a brickred solid, mp 169-171°C, rf (EtOAc) 0.43.

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Example II

[0039] (3-Amino-6-methoxy-benzofuran-2-yl)-(3-nitro-phenyl)-methanone

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40 Equivalent amounts, 5 g (33.5 mmol) of 2-Hydroxy-4-methoxy-benzenonitrile and 8.2 g (33.5 mol) of ω -Bromo-3-nitroacetophenone were dissolved in 30 ml DMF and 4.6 ml triethylamine were added. The mixture was heated to 75°C for 90 min, quenched with water and extracted 3 times with dichloromethane. The solvent was distilled off in vacuo and the residue dried over night. The crude product was heated under reflux in a mixture of 150 mg sodium in 50 ml ethanol for 90 min. After cooling to room temperature the solvent was distilled off, the residue solved in water and extracted 3 times with ethylacetate. The organic layer was dried over Na_2SO_4 , concentrated in vacuo and the residue was further purified by chromatography (silica gel 60).

45 Yield: 9.6 g (92%)
R_f: 0.18 (III)
Melting point: 214°C

[0040] The compounds shown in tables I-V are prepared in analogy to the procedure of example I.

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Table I:

Chemical Structure:

$$\text{2-(NHR')-3-D-4-oxo-4H-chromene}$$

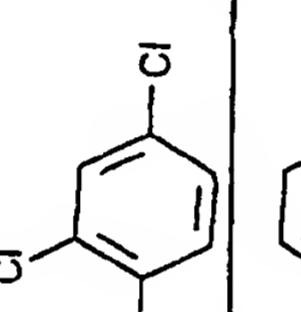
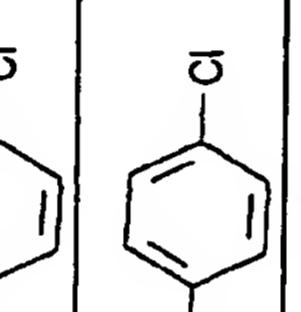
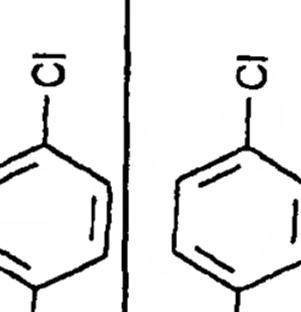
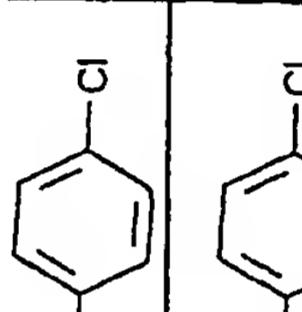
Ex.-No.	D	R ¹	R ⁴	Mp. (°C)	Yield (% of theory)	R _f *
III	-OCH ₃	-CO-CH ₃		202	100	0,39 (V)
IV	-OCH ₃	H		162	57	0,73 (V)
V	-OCH ₃	-CO-CO ₂ CH ₃		190	34	0,43 (VI)
VI	-OCH ₃	-CO ₂ CH ₃		107	9	63 (VI)
VII	-OCH ₃	-CO-CO ₂ H		166	32	0,09 (V)

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Table I: (continuation)

Ex.-No.	D	R ¹	R ⁴	Mp. (°C)	Yield (% of theory)	R _f *
VIII	-OCH ₃	-CH ₃		119-121	30	0,62 (IV)
IX	-OCH ₃	-CO-CO ₂ C ₂ H ₅		159	70	0,53 (VI)
X	-OCH ₃	-CO-CO ₂ H		199	87	0,07 (V)
XI	-OCH ₃	H		183	99	0,69 (VII)
XII	-OCH ₃	-CO-CH ₃		179	70	0,87 (V)
XIII	-OCH ₃	-CO-(CH ₂) ₂ -CH ₃		131,5	60	0,57 (V)
XIV	-OCH ₃			124,5	54	0,62 (VII)

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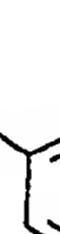
Table I: (continuation)

Ex.-No.	D	R ¹	R ⁴	Mp. (°C)	Yield (% of theory)	R _f *
XV	-OCH ₃	-CO-C ₆ H ₄ -CO ₂ CH ₃	C ₆ H ₄ -Cl	238	41	0,43 (VI)
XVI	-OCH ₃	-CO-C ₆ H ₄ -CO ₂ CH ₃	C ₆ H ₄ -Cl	202	50	0,41 (VI)
XVII	-OCH ₃	-CO-C ₆ H ₄ -CO ₂ H	C ₆ H ₄ -Cl	308	11	0,32 (V)
XVIII	-OCH ₃	-CO-C ₆ H ₄ -CO ₂ H	C ₆ H ₄ -Cl	279	4,5	0,37 (V)
XIX	-OCH ₃	-CO-C ₆ H ₄ -OCH ₃	C ₆ H ₄ -Cl	206	72	0,59 (VI)
XX	-OCH ₃	-CO-C ₆ H ₄ -OCH ₃	C ₆ H ₄ -Cl	177	80	0,58 (VI)

Table I: (continuation)

Ex.-No.	D	R ¹	R ⁴	M.p. (°C)	Yield (% of theory)	R _f *
XXI	-OCH ₃			155 (dec)	74	0,1 (VI)
XXII	-OCH ₃			163	72	0,44 (VII)
XXIII	-OCH ₃			139	44	0,44 (V)
XXIV	-OCH ₃			177	84	0,64 (VI)
XXV	-OCH ₃			230	64	0,77 (V)
XXVI	-OCH ₃	H		238	91	0,66 (IV)

Table I: (continuation)

Ex.-No.	D	R ¹	R ⁴	Mp. (°C)	Yield (% of theory)	R _f *
XXVII	-OCH ₃	-CO-CH ₂ -CO ₂ C ₂ H ₅		129	16	0,92 (V)
XXVIII	-OCH ₃	H		122	82	0,62 (IV)
XXIX	-OCH ₃	H		149-151	56	0,64 (IV)
XXX	-OCH ₃	H		135	30	0,6 (I)
XXXI	-OCH ₃	H		123	89	0,7 (I)
XXXII	-OCH ₃	H		136	41	0,8 (I)

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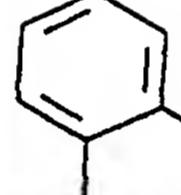
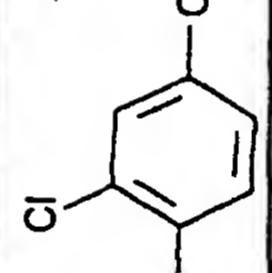
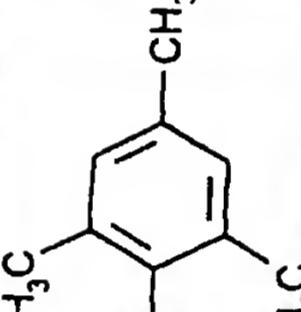
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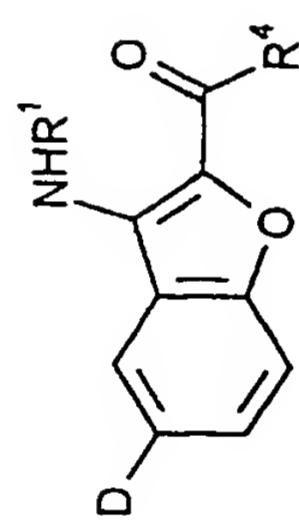
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Table I: (continuation)

Ex.-No.	D	R ¹	R ⁴	Mp. (°C)	Yield (% of theory)	R _f *
XXXIII	-OCH ₃	H		137	47	0,3 (III)
XXXIV	-OH	H		19		0,56 (IV)
XXXV	-OCH ₃	H		214	90	0,67 (IV)

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Table II



Ex.-No.	D	R ¹	R ⁴	M.p. (°C)	Yield (% of theory)	R _f *
XXXVI	OCH ₃	H	Cl 	90	90	0,1 (VI)
XXXVII	OCH ₃	H		155	62	0,4 (VI)
XXXVIII	OCH ₃	H		170	quant.	0,6 (VI)
XXXIX	OCH ₃	H		220	9	0,65 (VI)
XL	OCH ₃	H		258	63	0,33 (I)

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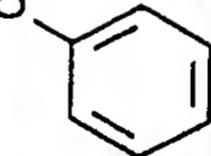
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Table II: (continuation)

Ex.-No.	D	R ¹	R ⁴	M.p. (°C)	Yield (% of theory)	R _f *
XLI	OCH ₃	H		130	61	0,4 (I)

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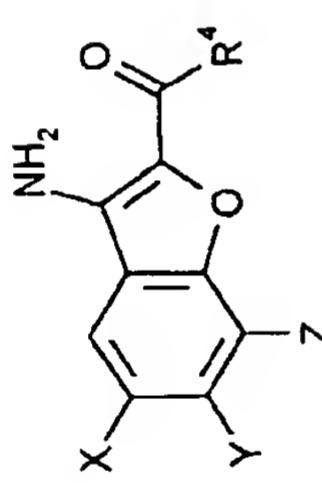
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Table III:



Ex.-No.	X	Y	Z	R ⁴	Mp. (°C)	Yield (% of theory)	R _f
XLII	H	COCH ₃	H	Cl — C6H4 — Cl	209	19	0.72 (V)
XLIII	H	COCH ₃	H	Br — C6H4 — Br	198	37	0.7 (V)
XLIV	H	NHSO ₂ — C6H4	H	Cl — C6H4 — Cl	223	25	0.71 (V)
XLV	H	COOCH ₃	H	Br — C6H4 — Br	253	30	0.72 (V)

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Table III: (continuation)

Ex.-No.	X	Y	Z	R ⁴	Mp. (°C)	Yield (% of theory)	R _f
XLVI	H	COOCH ₃	H		258	51	0.70 (V)
XLVII	H		H		210	72	0.67 (V)
XLVIII	H	CF ₃	H				
XLIX	H	CN	H				
L	H	NO ₂	H				
LI	H	CH ₃	H				

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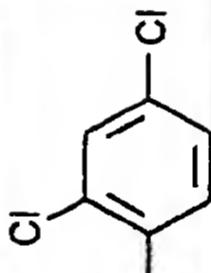
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Table III: (continuation)

Ex.-No.	X	Y	Z	R ⁴	Mp. (°C)	Yield (% of theory)	R _f
LII	H	OCH ₃	H				

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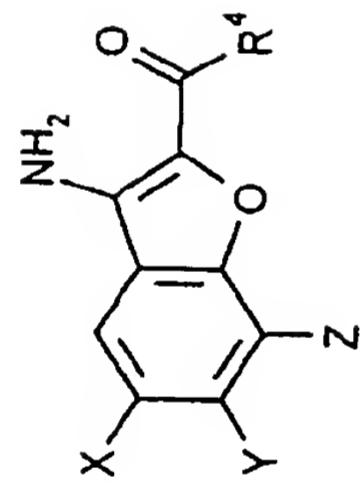
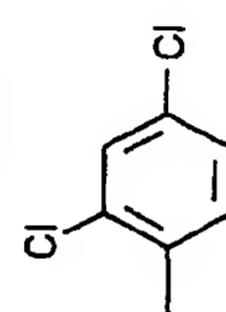
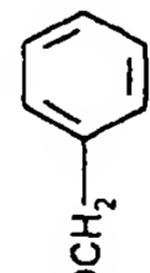
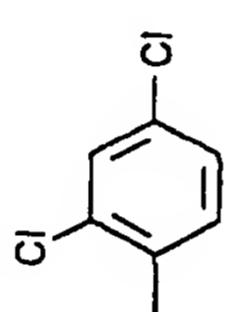
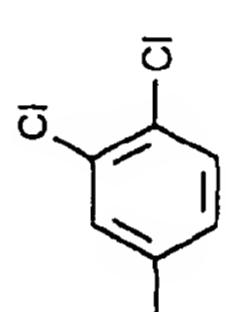
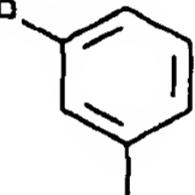


Table IV:

Ex.-No.	X	Y	Z	R ⁴	Mp. (°C)	Yield (% of theory)	R _f
LIII	H	H	OCH ₃	Cl-phenyl	210	57	0.4 (III)
LIV	H	H	OCH ₃	Br-phenyl	157	41	0.44 (III)
LV	OCH ₃	H	H	CH ₃ -phenyl	147	69	0.78 (V)

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Table IV: (continuation)

Ex.-No.	X	Y	Z	R ⁴	Mp. (°C)	Yield (% of theory)	R _f
LVI	Cl	OCH ₃	H		214	62	0.4 (V)
LVII	H	-OCH ₂ - 	H		150	46	0.5 (V)
LVIII	OCH ₃	H	H		178	68	0.7 (V)
LIX	OCH ₃	H	H		125	39	0.78 (V)

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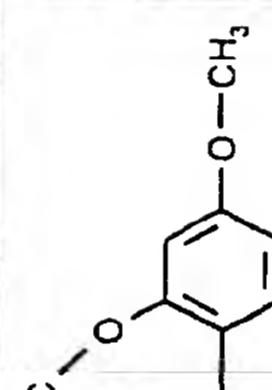
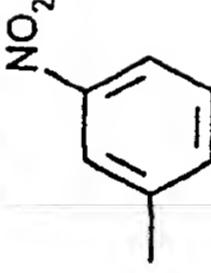
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Table IV: (continuation)

Ex.-No.	X	Y	Z	R ⁴	Mp. (°C)	Yield (% of theory)	R _f
LX	OCH ₃	H	H		127	59.4	0.65 (V)
LXI	OCH ₃	H	H		171	47	0.83 (V)

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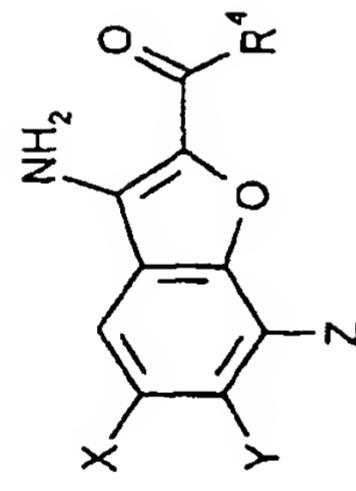
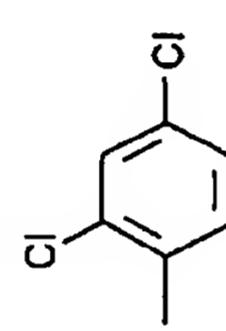
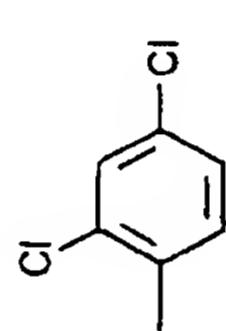
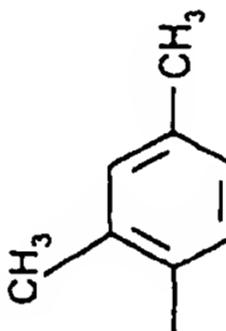
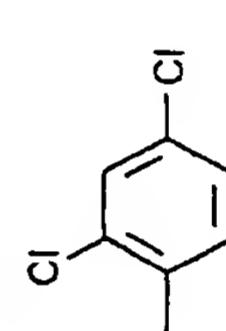


Table V:

Ex.-No.	X	Y	Z	R	Mp. (°C)	Yield (% of theory)	R _f
LXII	H	-OCH ₂ -pyridin-3-yl	H				
LXIII			H				
LXIV			H				

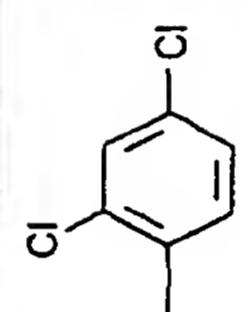
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Table V: (continuation)

Ex.-No.	X	Y	Z	R	Mp. (°C)	Yield (% of theory)	R _f
LXV	H	OCF ₃	H				
LXVI	H	NH ₂	H				
LXVII	H	OCH ₃	H		155	18	0.5 (III)
LXVIII	H	CONH ₂	H				

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Table V: (continuation)

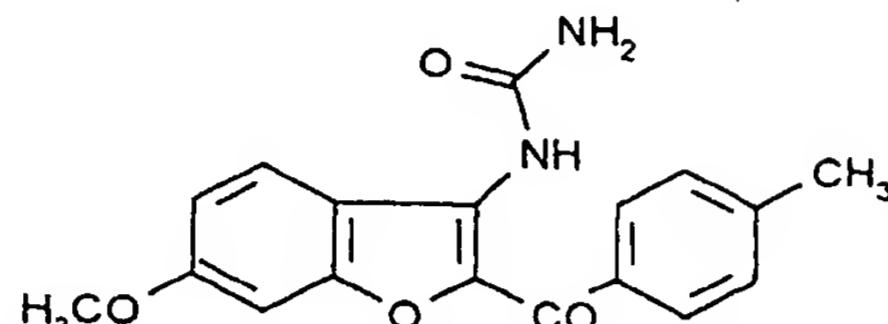
Ex.-No.	X	Y	Z	R	Mp. (°C)	Yield (% of theory)	R _f
LXIX	H	OC ₂ H ₄ OH	H				

Preparation Examples**Example 1**

5 [0041] N-(3-(6-methoxy-2-(4'-methylbenzoyl)benzofuranyl)urea

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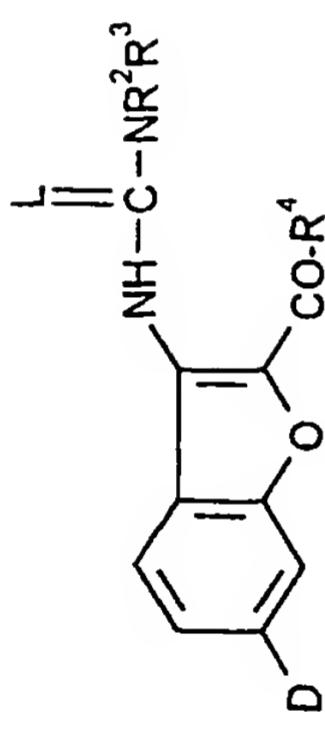
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Table 1:



Ex.-No.	D	L	R ²	R ³	R ⁴	Yield (% of theory)	Mp. (°C)	R _f *
2	-OCH ₃	O	H	H	Cl Cl-phenyl	82	218 (dec)	0,2 (V)
3	-OCH ₃	O	H	H	Br Cl-phenyl	92	264	0,54 (V)
4	-OCH ₃	O	H	H	Cl F-phenyl	87	266	0,55 (V)
5	-OCH ₃	O	H	H	F NO ₂ -phenyl	14	206-7	0,65 (V)
6	-OCH ₃	O	H	H		59	23	0,2 (V)
7	H ₃ CO ₂ C-O	O	H	H	Cl Cl-phenyl	53	208-9	0,6 (V)

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Table 1: (continuation)

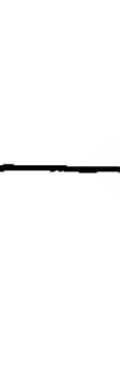
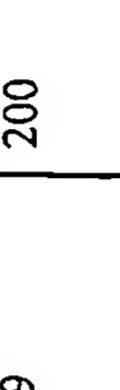
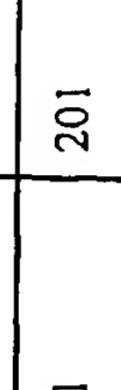
Ex.-No.	D	L	R ²	R ³	R ⁴	Yield (%) of theory	M.p. (°C)	R _r *
8	HO	O	H	H		65	337-9	0,12 (V)
9	H ₃ C-O	O	H	-CH ₃		56	174	0,87 (V)
10	H ₃ C-O	O	-CH ₃	-CH ₃		22	204	0,7 (V)
11	H ₃ C-O	O	H	H		41	217	0,62 (IV)
12	H ₃ C-O	O	H	H		89	200	0,5 (I)
13	H ₃ C-O	O	H	H		91	201	0,4 (I)
14	H ₃ C-O	O	H	H		93	212	0,2 (III)

Table 1: (continuation)

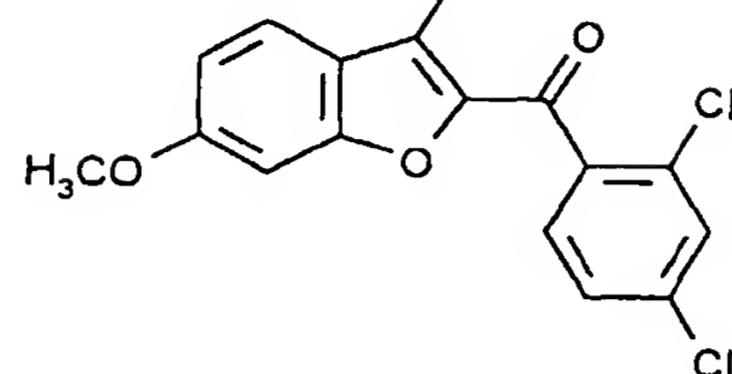
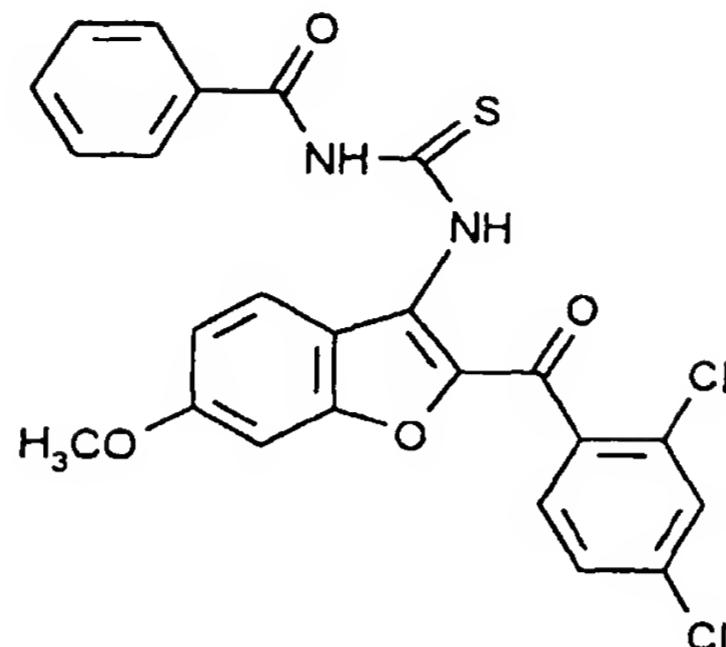
Ex.-No.	D	L	R ²	R ³	R ⁴	Yield (%) of theory	Mp. (°C)	R _f *
15	H ₃ C-O	O	H	H		67	204	0,2 (III)
16	H ₃ C-O	O	H	H		63	187	0,7 (V)
17	H ₃ C-O	O	H	-CH ₂ -C≡C-		54	174	0,9 (V)
18	H ₃ C-O	O	H			100	142	0,49 (II)
19	H ₃ C-O	O	H	-CH ₂ -C≡C-		16	207	0,21 (II)
20	H ₃ C-O	O				18	187	0,89 (V)

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Example 21

[0043] N-benzoyl-N'-(3-(2-(2',4'-dichlorobenzoyl)-6-methoxybenzofuranyl)thiourea

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20 1.35 g (4 mmol) of the compound from example IV and benzoylisothiocyanate (720 mg; 4.4 mmol) were refluxed in acetone (20 ml) for 24 h, after which time the reaction was cooled and poured onto iced water with stirring. The precipitate was isolated by filtration and washed with water. After drying, in a desiccator under vacuum, the title compound was isolated (1.6 g; 3.3 mmol; 84% yield) as a yellow solid, mp 100-102°C, rf 0,67 (IV).

[0044] The compounds shown in table 2-6 were prepared in analogy to the procedure of example 1:

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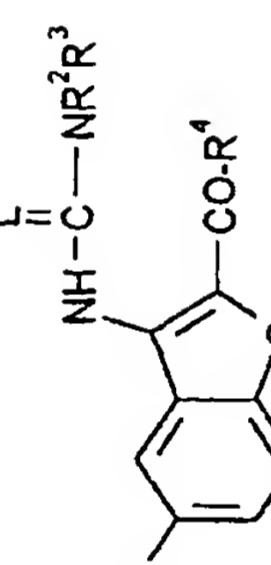
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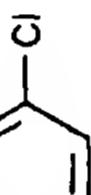
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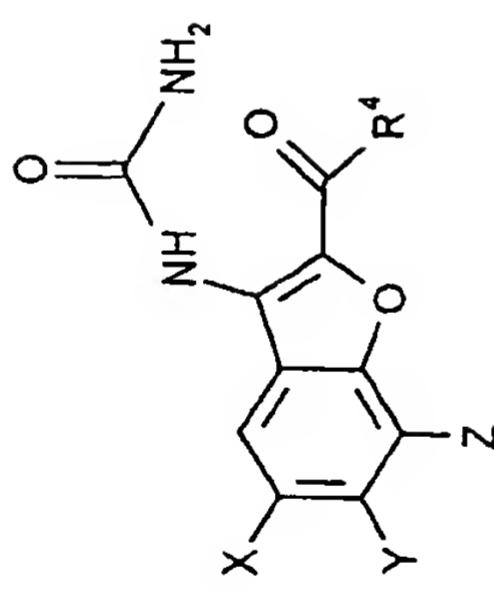
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Table 2:

 $\text{NH}-\overset{\text{L}}{\underset{\text{II}}{\text{C}}}-\text{NR}^2\text{R}^3-\text{CO-R}^4$

Ex.-No.	D	L	R ²	R ³	R ⁴	Yield (% of theory)	M.p. (°C)	R _f *
22	OCH ₃	O	H	H		49	228 (dec.)	0.34 (I)
23	OCH ₃	O	H	H		29.5	231 (dec.)	0.42 (I)
24	OCH ₃	O	H	H		63	258	0.33 (I)
25	OCH ₃	O	H	H		50.4	222	0.33 (I)
26	OCH ₃	O	H	H		9	217	0.36 (I)
27	OCH ₃	O	H	H		33.5	214	0.4 (I)

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Table 3:



Ex.-No.	X	Y	Z	R ⁴	Mp. (°C)	Yield (% of theory)	R _f
28	H	H	OCH ₃	Cl-phenyl	250 (Z)	46	0.7 (V)
29	H	H	OCH ₃	Bromo-phenyl	226 (Z)	98	0.04 (III)
30	OCH ₃	H	H	CH ₃ -phenyl	266	64	0.54 (V)

Table 3: (continuation)

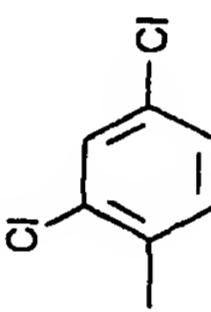
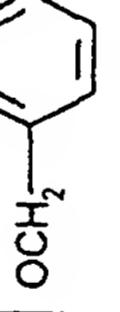
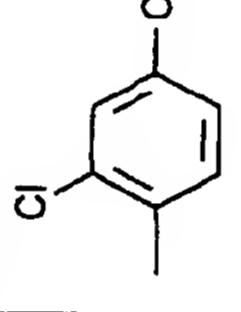
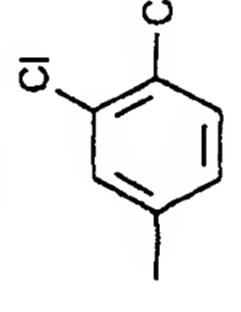
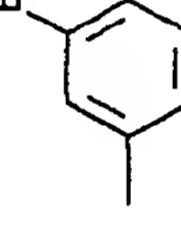
Ex.-No.	X	Y	Z	R ⁴	Mp. (°C)	Yield (% of theory)	R _f
31	Cl	OCH ₃	H		-	89	0.6 (V)
32	H		H		193	96	0.83 (V)
33	OCH ₃	H	H		246	89	0.56 (V)
34	OCH ₃	H	H		217	30	0.61 (V)

Table 3: (continuation)

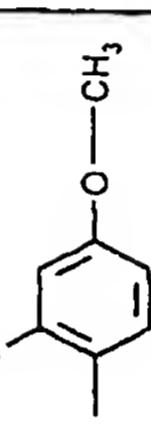
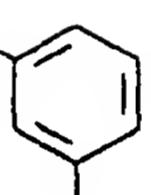
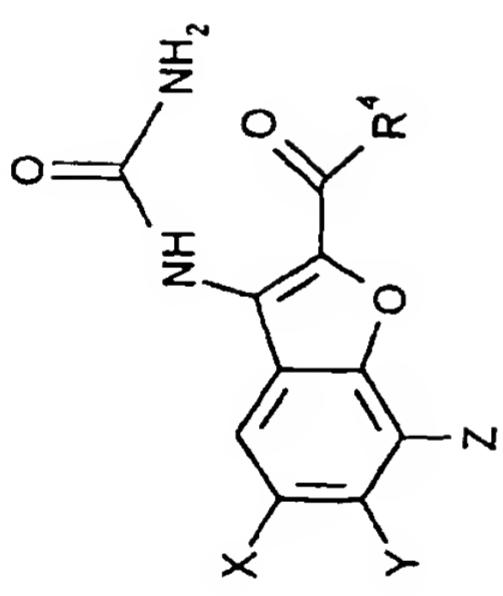
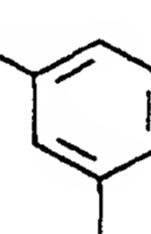
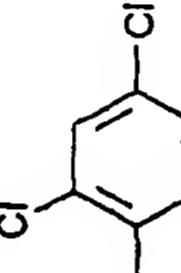
Ex.-No.	X	Y	Z	R ⁴	M.p. (°C)	Yield (% of theory)	R _f
35	OCH ₃	H	H ₃ C—O— 		202	50	0.52 (V)
36	OCH ₃	H	H		234	79	0.41 (V)

Table 4:



Ex.-No.	X	Y	Z	R ⁴	Mp. (°C)	Yield (% of theory)	R _f
37	H	COCH ₃	H		195	35	0.3 (III)
38	H	COCH ₃	H		-	27	0.34 (III)
39	H		H			17	0.54 (III)

Table 4: (continuation)

Ex.-No.	X	Y	Z	R ⁴	Mp. (°C)	Yield (% of theory)	R _f
40	H	COOCH ₃	H		146	35	0.88 (V)
41	H	COOCH ₃	H		245	37	0.77 (V)
42	H	NHSO ₂ 	H		221	20	0.44 (V)
43	H	CF ₃	H				

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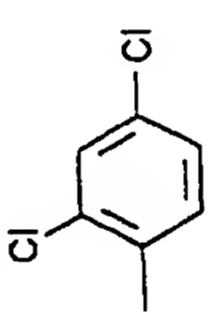
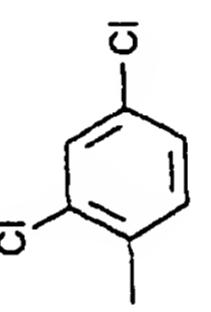
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Table 4: (continuation)

Ex.-No.	X	Y	Z	R ⁴	Mp. (°C)	Yield (% of theory)	R _f
44	H	CN	H				
45	H	NO ₂	H				

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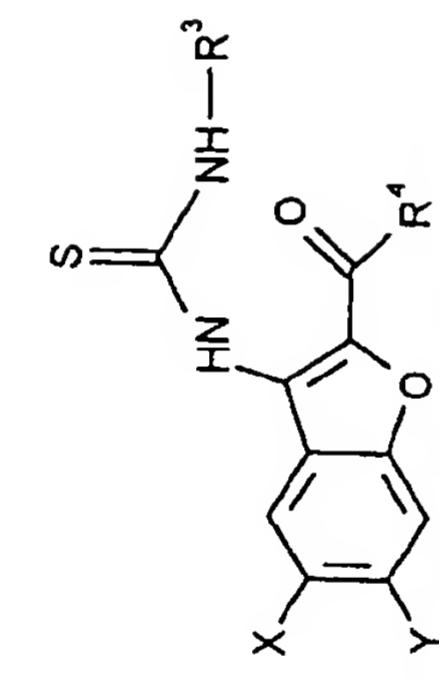


Table 5:

Ex.-No.	R ³	R ⁴	X	Y	Yield (% of theory)	R _f
46	COOC ₂ H ₅	Cl — C ₆ H ₄ — Cl	OCH ₃	H	62	0.34 (V)
47	COOC ₂ H ₅	Cl — C ₆ H ₄ — Cl	H	OCH ₃	56	0.38 (VII)

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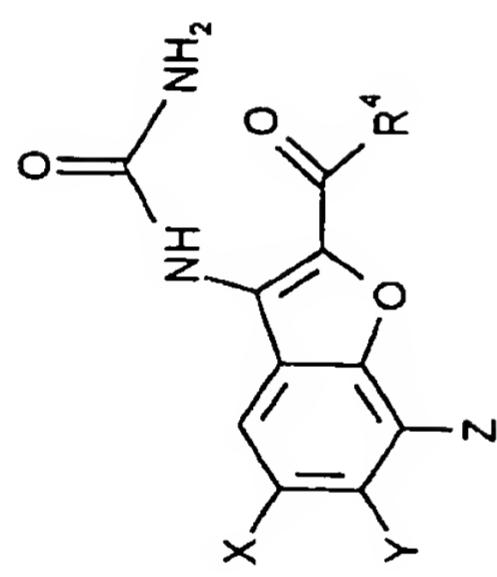
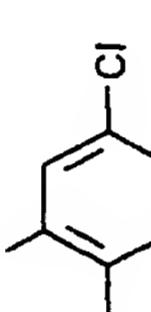


Table 6:

Ex.-No.	X	Y	Z	R ⁴	Mp. (°C)	Yield (% of theory)	R _f
48	H	OCH ₂ -pyridin-2-yl	H	Cl-phenyl			
49			H	Cl-phenyl			
50			H	Cl-phenyl			

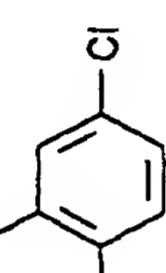
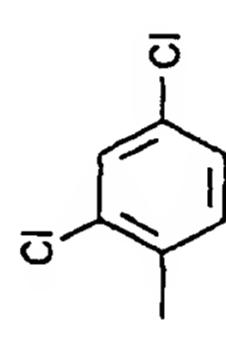
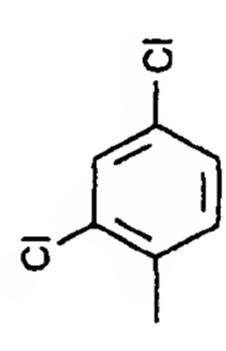
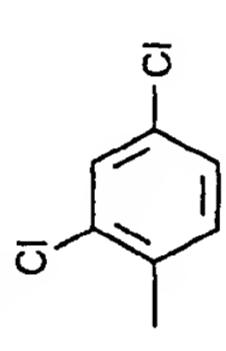
Table 6: (continuation)

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Ex.-No.	X	Y	Z	R ⁴	M.p. (°C)	Yield (% of theory)	R _f
51	H	CH ₃	H		224	31	0.5 (V)
52	H	OCF ₃	H				
53	H	NH ₂	H				
54	H	OCH ₃	H		217	70	0.27 (III)

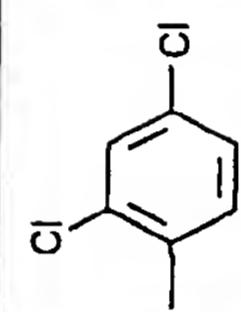
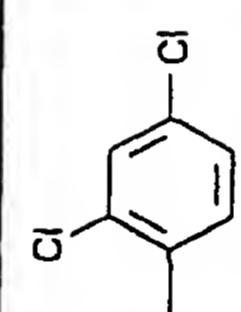
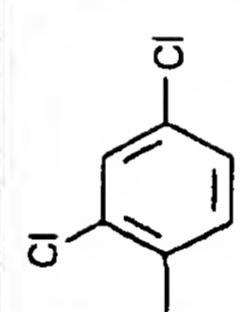
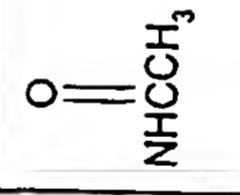
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Table 6: (continuation)

Ex.-No.	X	Y	Z	R ⁴	Mp. (°C)	Yield (% of theory)	R _f
55	H	CONH ₂	H				
56	H	OC ₂ H ₄ OH	H				
57	H	OCH ₂ CO ₂ CH ₃	H				
58	H	OSO ₂ CH ₃	H				

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Table 6: (continuation)

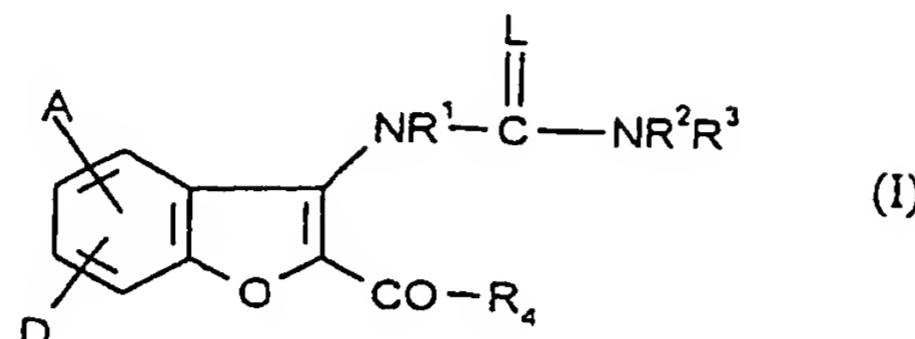
Ex.-No.	X	Y	Z	R ⁴	Mp. (°C)	Yield (% of theory)	R _f
59	H	OCH(CH ₃) ₂	H				
60							
61			H				

Claims

1. N-(3-benzofuranyl)urea-derivatives of the general formula (I)

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in which

A and D

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are identical or different and represent hydrogen, straight-chain or branched acyl or alkoxy carbonyl, each having up to 6 carbon atoms, or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by carboxyl or alkoxy carbonyl having up to 6 carbon atoms, phenoxy or benzoyl, or represent halogen, carboxyl, cyano, nitro, trifluoromethyl, trifluoromethoxy or a group of a formula -OR⁵, -S(O)_aR⁶, -(O-CH₂-CO)_b-NR⁷R⁸, -CO-NR⁹R¹⁰, -SO₂-NR¹¹R¹² or -NH-SO₂R¹³,

in which

25

R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹ and R¹²

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are identical or different and denote hydrogen, cycloalkyl having 3 to 6 carbon atoms, benzyl or a 5 to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the series comprising N, S and O and to which a phenyl ring can be fused and which is optionally substituted by identical or different substituents from the series comprising halogen, cyano, nitro or by a straight-chain or branched alkyl having up to 6 carbon atoms or denote straight-chain or branched alkyl, alkenyl or acyl each having up to 8 carbon atoms, or denote phenyl, which is optionally monosubstituted to disubstituted by identical or different substituents from the series comprising

35

nitro, halogen, carboxy or straight-chain or branched alkoxy carbonyl having up to 6 carbon atoms,

40

or

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R⁵ denotes a hydroxyl protecting group or straight-chain or branched alkoxy carbonyl having up to 6 carbon atoms, or denotes straight-chain or branched alkyl having up to 8 carbon atoms, which is substituted by carboxyl, hydroxyl, straight-chain or branched acyl or alkoxy carbonyl each having up to 6 carbon atoms, phenoxy, benzoyl or by a 5 to 7-membered unsaturated heterocycle having up to 3 hetero atoms from the series comprising N, S and/or O, which is optionally substituted by halogen, cyano, nitro or by straight-chain or branched alkyl having up to 6 carbon atoms

50

or

55

R⁵ denotes a group of a formula SO₂R¹⁴,
in which

R¹⁴ denotes phenyl, trifluoromethyl or straight-chain or branched alkyl having up to 4 car-

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bon atoms,

5 a denotes a number 0, 1 or 2,
b denotes a number 0 or 1,
R⁷ denotes hydrogen or a straight-chain or branched alkyl having up to 4 carbon atoms,
R¹³ denotes aryl having up 6 to 10 carbon atoms, trifluoromethyl or straight-chain or branched alkyl having up to 6 carbon atoms,

10 R¹ represents hydrogen, straight-chain or branched alkyl having up to 6 carbon atoms, an aminoprotecting group or a group of the formula -CO-R¹⁵,
in which

15 R¹⁵ denotes hydroxyl, straight chain or branched alkoxy carbonyl having up to 6 carbon atoms, cycloalkyl having up 3 to 6 carbon atoms, pyridyl, pyrrolidinyl or straight chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by halogen, carboxyl or straight chain or branched alkoxy carbonyl having up to 6 carbon atoms, or
denotes phenyl, which is optionally substituted by hydroxyl, carboxyl or straight chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,

20 L represents an oxygen or sulfur atom,

25 R² and R³ are identical or different and represent hydrogen, cycloalkyl having up to 6 carbon atoms, straight chain or branched alkyl, alkoxy carbonyl or alkenyl each having up to 8 carbon atoms, or represent benzoyl or aryl having 6 to 10 carbon atoms, which are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising halogen, cyano, nitro, carboxyl, straight-chain or branched alkyl, alkoxy, alkoxy carbonyl or acyl each having up to 6 carbon atoms,
or

30 R² and R³ together with the nitrogen atom form a 5- to 7-membered saturated heterocycle optionally having a further O atom,
and

35 R⁴ represents phenyl, which is optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, thiophenyl, cycloalkyl having up to 3 to 6 carbon atoms, halogen, nitro, tetrazolyl, thiazolyl, furanyl, pyridyl, trifluoromethyl, difluoromethyl, cyano, carboxyl, straight-chain or branched alkyl, alkoxy, alkoxy carbonyl or acyl each having up to 8 carbon atoms, or phenyl is optionally substituted by phenyl, which is optionally monosubstituted to disubstituted by halogen, or
by a group of a formula -NR¹⁶R¹⁷, -SR¹⁸, SO₂R¹⁹ or -O-SO₂R²⁰,
in which

40 R¹⁶ and R¹⁷ have the abovementioned meaning of R⁷ and R⁸ and are identical or different to the latter,
or

45 R¹⁶ denotes hydrogen,
and

50 R¹⁷ denotes straight-chain or branched acyl having up to 6 carbon atoms,
R¹⁸ denotes hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,
R¹⁹ and R²⁰ are identical or different and represent straight-chain or branched alkyl having up to 6 carbon atoms, benzyl or phenyl,
and salts thereof.

55 2. N-(3-benzofuranyl)urea-derivatives of the formula according to claim 1,

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in which

A and D are identical or different and represent hydrogen, straight-chain and branched acyl or alkoxy carbonyl each having up to 5 carbon atoms or straight-chain or branched alkyl having up to 4 carbon atoms which is optionally substituted by carboxyl, hydroxyl, alkoxy carbonyl having up to 5 carbon atoms, phenoxy or benzoyl, or represent fluorine, chlorine, bromine, nitro, trifluoromethyl or a group of a formula -OR⁵, -S(O)_a-R⁶, (O-CH₂-CO)_b-NR⁷R⁸, -CO-NR⁹R¹⁰, -SO-NR¹¹R¹² or -NH-SO₂-R¹³, in which

10 R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹ and R¹² are identical or different and denote hydrogen, cyclopropyl, cyclopentyl, cyclohexyl, chinolyl, pyridyl, imidazolyl, 1,3-thiazolyl or thienyl, which are optionally substituted by identical or different substituents from the series comprising fluorine, chlorine, bromine, iodine, cyano, nitro or by a straight-chain or branched alkyl having up to 5 carbon atoms,

15 R⁷ denote straight-chain or branched alkyl, alkenyl or acyl each having up to 6 carbon atoms, or

20 R⁸ denote phenyl, which is optionally monosubstituted to disubstituted by identical or different substituents from the series comprising nitro, fluorine, chlorine, bromine, iodine, carboxyl or straight-chain or branched alkoxy carbonyl having up to 5 carbon atoms,

25 or

30 R⁵ denotes benzyl, acetyl or tetrahydropyranyl or straight chain or branched alkoxy carbonyl having up to 4 carbon atoms, denotes straight-chain or branched alkyl having up to 6 carbon atoms, which is substituted by carboxyl, hydroxyl, straight-chain or branched acyl or alkoxy carbonyl each having up to 4 carbon atoms, phenoxy, benzoyl or by pyridyl, imidazolyl, thienyl or furyl, which are optionally substituted by fluorine, chlorine, bromine, cyano, nitro or by straight-chain or branched alkyl having up to 4 carbon atoms,

35 or

40 R⁵ denotes a group of a formula -SO₂-R¹⁴, in which

45 R¹⁴ denotes phenyl, trifluormethyl or straight-chain or branched alkyl having up to 3 carbon atoms,

a denotes a number 0, 1 or 2,

b denotes a number 0 or 1,

50 R⁷ denotes hydrogen or a straight-chain or branched alkyl having up to 3 carbon atoms,

R¹³ denotes phenyl, trifluormethyl or straight-chain or branched alkyl having up to 3 carbon atoms,

55 R¹ represents hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms, tert.butoxycarbonyl or a group of the formula -CO-R¹⁵ in which

R¹⁵ denotes hydroxyl, straight chain or branched alkoxy carbonyl having up to 4 carbon atoms, cyclopentyl, cyclohexyl, pyridyl, pyrrolidinyl or straight chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by fluorine, chlorine, bromine, carboxyl or straight chain or branched alkoxy carbonyl having up to 4 carbon atoms, or

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denotes phenyl, which is optionally substituted by hydroxyl, carboxyl or straight chain or branched alkoxy or alkoxy carbonyl each having up to 4 carbon atoms,

5 L represents an oxygen or sulfur atom,

R² and R³ are identical or different and represent hydrogen, cyclobutyl, cyclopentyl, cyclohexyl or straight-chain or branched alkyl, alkoxy carbonyl or alkenyl each having up to 6 carbon atoms, or 10 represent benzoyl or phenyl, which are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising fluorine, chlorine, bromine, iodine, carboxyl, cyano, nitro or by a straight-chain or branched alkyl, alkoxy or alkoxy carbonyl each having up to 5 carbon atoms,

or

15 R² and R³ together with the nitrogen atom form a pyrrolidinyl, piperidinyl or morpholinyl ring,

and

20 R⁴ represents phenyl, which is optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, thiophenyl, cyclopentyl, cyclohexyl, fluorine, chlorine, bromine, iodine, nitro, tetrazolyl, thiazolyl, furanyl, pyridyl, trifluoromethyl, difluoromethyl, cyano, carboxyl, straight-chain or branched alkyl, alkoxy, alkoxy carbonyl or acyl each having up to 6 carbon atoms, or 25 phenyl is optionally substituted by phenyl, which is optionally monosubstituted to disubstituted by fluorine, chlorine or bromine,

and salts thereof.

3. N-(3-benzofuranyl)urea-derivatives of the formula according to claim 1, in which

30 A and D are identical or different and represent hydrogen, straight-chain or branched acyl or alkoxy carbonyl each having up to 4 carbon atoms, or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by carboxyl or alkoxy carbonyl having up to 4 carbon atoms, phenoxy or benzoyl, or represent 35 fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl, trifluormethoxy, or a group of a formula -OR⁵, -S(O)_aR⁶, -(O-CH₂-CO)_b-NR⁷R⁸, -CO-NR⁹R¹⁰, -SO₂-NR¹¹R¹² or -NH-SO₂R¹³, in which

40 R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹ and R¹²

are identical and denote hydrogen, cyclopropyl, cyclopentyl, cyclohexyl, chinolyl, pyridyl, imidazolyl, 1,3-thiazolyl or thienyl, which are optionally substituted by identical or different substituents from the series comprising fluorine, chlorine, bromine, iodine, cyano, nitro or by a straight-chain or branched alkyl having up to 3 carbon atoms, 45 denote straight-chain or branched alkyl, alkenyl or acyl each having up to 3 carbon atoms, or denote phenyl, which is optionally monosubstituted to disubstituted by identical or different substituents from the series comprising nitro, fluorine, chlorine, bromine, iodine, carboxyl or straight-chain or branched alkoxy carbonyl having up to 3 carbon atoms,

50 or

55 R⁵ denotes benzyl, acetyl or tetrahydropyranyl or straight-chain or branched alkoxy carbonyl having up to 3 carbon atoms, denotes straight-chain or branched alkyl having up to 4 carbon atoms, which is substituted by carboxyl, hydroxyl, straight-chain or branched acyl or alkoxy carbonyl each having up to 3 carbon

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atoms, phenoxy, benzoyl or by pyridyl, imidazolyl or thienyl,

or

5 R⁵ denotes a group of a formula -SO₂-R¹⁴,
 in which
 R¹⁴ denotes phenyl, trifluormethyl or methyl.

10 a denotes a number 0, 1 or 2,
 b denotes a number 0 or 1,
 R⁷ denotes hydrogen, methyl or ethyl,
 R¹³ denotes phenyl, trifluoromethyl or methyl,

15 R¹ represents hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms or a group of the
 formula -CO-R¹⁵,
 in which

20 R¹⁵ denotes hydroxyl, straight chain or branched alkoxy carbonyl having up to 3 carbon atoms, cyclopentyl,
 cyclohexyl, pyridyl, pyrrolidinyl or straight chain or branched alkyl having up to 4 carbon atoms, which
 is optionally substituted by fluorine, chlorine, bromine, carboxyl or straight chain or branched alkoxy-
 carbonyl having up to 3 carbon atoms, or
 denotes phenyl, which is optionally substituted by hydroxyl, carboxyl or straight chain or branched
 alkoxy or alkoxy carbonyl each having up to 3 carbon atoms,

25 L represents an oxygen or sulfur atom,

30 R² and R³ are identical or different and represent hydrogen, cyclobutyl, cyclopentyl, cyclohexyl or straight-chain
 or branched alkyl, alkoxy carbonyl or alkenyl each having up to 5 carbon atoms, or
 represent benzoyl or phenyl, which are optionally monosubstituted to trisubstituted by identical or
 different substituents from the series comprising fluorine, chlorine, bromine, iodine, carboxy, cyano,
 nitro or by a straight-chain or branched alkyl, alkoxy or alkoxy carbonyl each having up to 3 carbon
 atoms,

35 or

40 R² and R³ together with the nitrogen atom form a pyrrolidinyl ring,
 and

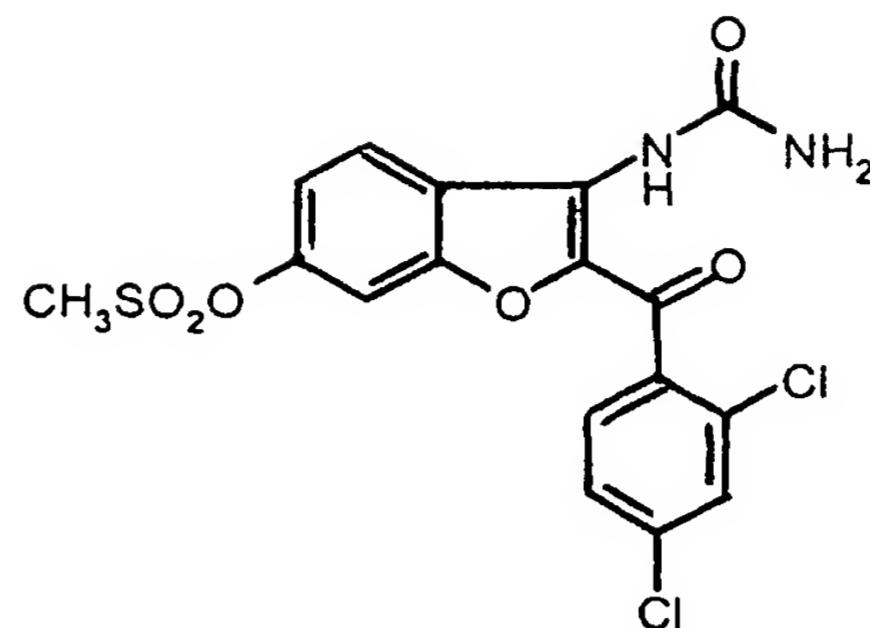
45 R⁴ represents phenyl, which is optionally monosubstituted to trisubstituted by identical or different substituents
 from the series comprising hydroxyl, thiophenyl, cyclopentyl, cyclohexyl, fluorine, chlorine, bromine, nitro,
 tetrazolyl, thiazolyl, furanyl, pyridyl, trifluoromethyl, difluoromethyl, cyano, carboxyl, straight-chain or
 branched alkyl, alkoxy, alkoxy carbonyl or acyl each having up to 5 carbon atoms, or
 phenyl is optionally substituted by phenyl, which is optionally monosubstituted to disubstituted by chlorine,
 and salts thereof.

50 4. The compound of the formula

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according to claim 1.

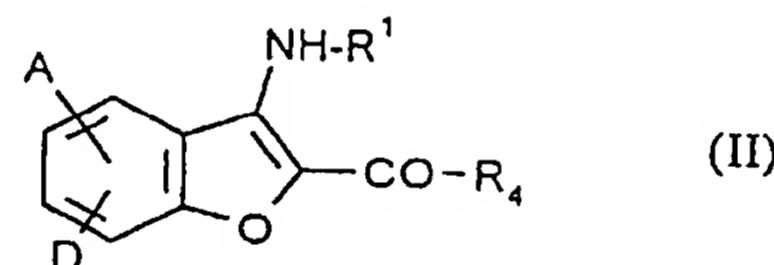
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5. N-(3-benzofuranyl)urea-derivatives according to claim 1 to 4 for therapeutic use.

25

6. The process for the preparation of N-(3-benzofuranyl)urea-derivatives according to claim 1 to 4 characterized in that compounds of the general formula (II)

30



in which

35

A, D, R¹ and R⁴ have the abovementioned meaning
are reacted with compounds of the general formula (III)

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L and R² in which
have the abovementioned meaning
in inert solvents, if appropriate in the presence of a base and/or in the presence of an auxiliary,
and in the case of R²/R³ = H and L = O compounds of the general formula (II) are reacted with
compounds of the general formula (IIIa)

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and in the case of R²/R³ = H and L = S,
compounds of the general formula (II) are reacted with NH₄SCN,
and in case of R¹, R² and/or R³ ≠ H the amino groups are derivated optionally by common methods.

7. The composition containing at least one N-(3-benzofuranyl)urea-derivative according to claim 1 to 4 and a pharmacologically acceptable diluent.

8. A composition according to claim 7 for the treatment of acute and chronic inflammatory processes.

9. The process for the preparation of compositions according to claim 7 and 8 characterized in that the N-(3-benzofuranyl)urea-derivative together with customary auxiliaries is brought into a suitable application form.

10. Use of N-(3-benzofuranyl)urea-derivatives according to claim 1 to 4 for the preparation of medicaments.

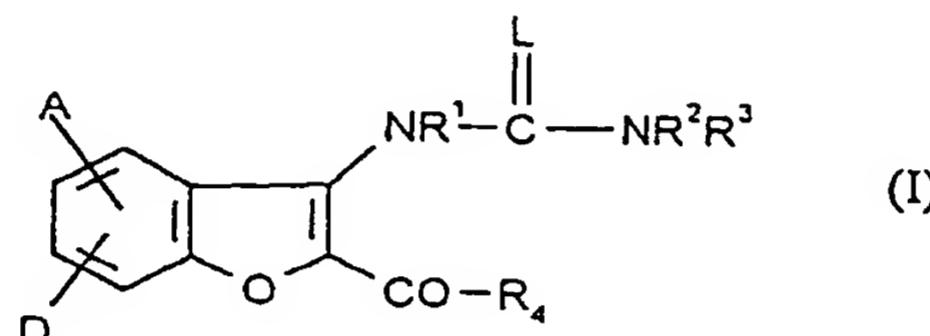
11. Use according to claim 10 for the preparation of medicaments for the treatment of acute and chronic inflammatory processes.

10

Patentansprüche

1. N-(3-Benzofuranyl)harnstoff-Derivate der allgemeinen Formel (I):

20



25

worin gilt:

A und D sind gleich oder verschieden und stellen Wasserstoff, einen geradkettigen oder verzweigten Acyl- oder Alkoxy carbonyl-Rest mit jeweils bis zu 6 Kohlenstoffatomen oder einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 6 Kohlenstoffatomen dar, der gegebenenfalls mit einem Carboxyl- oder Alkoxy carbonyl-Rest mit bis zu 6 Kohlenstoffatomen, einem Phenoxy- oder mit einem Benzoyl-Rest substituiert ist, oder sie stellen ein Halogenatom, eine Carboxyl-, Cyano-, Nitro-, Trifluormethyl-, Trifluormethoxy-Gruppe oder eine Gruppe der Formeln -OR⁵, -S(O)_aR⁶, -(O-CH₂-CO)_b-NR⁷R⁸, -CO-NR⁹R¹⁰, -SO₂-NR¹¹R¹² oder -NH-SO₂R¹³ dar,

35

worin gilt:

40

R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹ und R¹² sind gleich oder verschieden und bedeuten Wasserstoff, einen Cycloalkyl-Ring mit 3 bis 6 Kohlenstoffatomen, einen Benzyl-Rest oder einen 5- bis 7-gliedrigen gesättigten oder ungesättigten Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe aus N, S und O, woran ein Phenyl-Ring kondensiert sein kann und der gegebenenfalls mit gleichen oder verschiedenen Substituenten aus der Reihe aus einem Halogenatom, einer Cyano- und aus einer Nitro-Gruppe oder mit einem geradkettigen oder verzweigten Alkyl-Rest mit bis zu 6 Kohlenstoffatomen substituiert ist, oder sie bedeuten einen geradkettigen oder verzweigten Alkyl-, Alkenyl- oder Acyl-Rest mit jeweils bis zu 8 Kohlenstoffatomen, oder

45

sie bedeuten einen Phenyl-Rest, der gegebenenfalls mit gleichen oder verschiedenen Substituenten aus der Reihe aus einer Nitro-Gruppe, einem Halogenatom, einem Carboxy- oder aus einem geradkettigen oder verzweigten Alkoxy carbonyl-Rest mit bis zu 6 Kohlenstoffatomen mono-bis disubstituiert ist,

50

oder

55

R⁵ bedeutet eine Hydroxyl-Schutzgruppe oder einen geradkettigen oder verzweigten Alkoxy carbonyl-Rest mit bis zu 6 Kohlenstoffatomen, oder er bedeutet einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 8 Kohlenstoffatomen, der mit einem Carboxy-, Hydroxyl-, geradkettigen oder verzweigten Acyl- oder Alkoxy carbonyl-Rest mit jeweils bis zu 6 Kohlenstoffatomen, einem Phenoxy-, Benzoyl-Rest oder mit einem 5- bis 7-gliedrigen ungesättigten Heterocyclus mit bis zu 3 Heteroatomen aus der Reihe aus N, S und/oder O substituiert ist, der gegebenenfalls mit einem Halogenatom, einer Cyano-, Nitro-Gruppe oder mit einem geradkettigen oder verzweigten Alkyl-Rest mit bis zu 6 Kohlenstoffatomen substituiert ist,

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oder

R⁵ bedeutet eine Gruppe der Formel -SO₂R¹⁴,
worin

5 R¹⁴ einen Phenyl-, Trifluormethyl- oder einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 4 Kohlenstoffatomen bedeutet,

a bedeutet die Zahl 0, 1 oder 2,

b bedeutet die Zahl 0 oder 1,

10 R⁷ bedeutet Wasserstoff oder einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 4 Kohlenstoffatomen,
R¹³ bedeutet einen Aryl-Rest mit 6 bis 10 Kohlenstoffatomen, einen Trifluormethyl- oder einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 6 Kohlenstoffatomen,

R¹ stellt Wasserstoff, einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 6 Kohlenstoffatomen, eine Amino-Schutzgruppe oder eine Gruppe der Formel -CO-R¹⁵ dar,

15 worin gilt:

R¹⁵ bedeutet eine Hydroxyl-Gruppe, einen geradkettigen oder verzweigten Alkoxycarbonyl-Rest mit bis zu 6 Kohlenstoffatomen, einen Cycloalkyl-Ring mit 3 bis 6 Kohlenstoffatomen, einen Pyridyl-, Pyrrolidinyl- oder einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 8 Kohlenstoffatomen, der gegebenenfalls mit einem Halogenatom, einem Carboxyl- oder einem geradkettigen oder verzweigten Alkoxy- oder Alkoxycarbonyl-Rest mit jeweils bis zu 6 Kohlenstoffatomen substituiert ist, oder
er bedeutet einen Phenyl-Rest, der gegebenenfalls mit einer Hydroxyl-Gruppe, einem Carboxyl- oder einem geradkettigen oder verzweigten Alkoxy- oder Alkoxycarbonyl-Rest mit jeweils bis zu 6 Kohlenstoffatomen substituiert ist,

25 L stellt ein Sauerstoff- oder Schwefelatom dar,

R² und R³ sind gleich oder verschieden und stellen Wasserstoff, einen Cycloalkyl-Ring mit bis zu 6 Kohlenstoffatomen, einen geradkettigen oder verzweigten Alkyl-, Alkoxycarbonyl- oder einen Alkenyl-Rest mit jeweils bis zu 8 Kohlenstoffatomen dar, oder

30 sie stellen einen Benzoyl- oder Aryl-Rest mit 6 bis 10 Kohlenstoffatomen dar, welche gegebenenfalls mit gleichen oder verschiedenen Substituenten aus der Reihe aus einem Halogenatom, einer Cyano-, Nitro-Gruppe, einem Carboxyl-, geradkettigen oder verzweigten Alkyl-, Alkoxy-, Alkoxycarbonyl- oder aus einem Acryl-Rest mit jeweils bis zu 6 Kohlenstoffatomen mono- bis trisubstituiert sind,

35 oder

R² und R³ bilden zusammen mit dem Stickstoffatom einen 5- bis 7-gliedrigen gesättigten Heterocyclus, der gegebenenfalls des weiteren ein O-Atom aufweist,
und

40 R⁴ stellt einen Phenyl-Rest dar, der gegebenenfalls mit gleichen oder verschiedenen Substituenten aus der Reihe aus einer Hydroxyl-Gruppe, einem Thiophenyl-Rest, einem Cycloalkyl-Ring mit 3 bis 6 Kohlenstoffatomen, einem Halogenatom, einer Nitro-Gruppe, einem Tetrazolyl-, Thiazolyl-, Furanyl-, Pyridyl-, Trifluormethyl-, Difluormethyl-, Cyano-, Carboxyl-, geradkettigem oder verzweigten Alkyl-, Alkoxy-, Alkoxycarbonyl- oder aus einem Acryl-Rest mit jeweils bis zu 8 Kohlenstoffatomen mono- bis trisubstituiert ist, oder
der Phenyl-Rest ist gegebenenfalls mit einem Phenyl-Rest substituiert, der gegebenenfalls mit einem Halogenatom oder mit einer Gruppe der Formel -NR¹⁶R¹⁷, -SR¹⁸, -SO₂R¹⁹ oder -O-SO₂R²⁰ mono- bis disubstituiert ist,

45 worin gilt:

50 R¹⁶ und R¹⁷ haben die oben angegebene Bedeutung von R⁷ und R⁸ und sind gleich oder verschieden von einander,

oder

R¹⁶ bedeutet Wasserstoff,
und

55 R¹⁷ bedeutet einen geradkettigen oder verzweigten Acyl-Rest mit bis zur 6 Kohlenstoffatomen,
R¹⁸ bedeutet Wasserstoff oder einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 6 Kohlenstoffatomen,

R¹⁹ und R²⁰ sind gleich oder verschieden und stellen einen geradkettigen oder verzweigten Alkyl-Rest mit bis

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zu 6 Kohlenstoffatomen, einen Benzyl- oder einen Phenyl-Rest dar,

und Salze davon.

5 2. N-(3-Benzofuranyl)harnstoff-Derivate der Formel gemäß Anspruch 1,
 worin gilt:

10 A und D sind gleich oder verschieden und stellen Wasserstoff, einen geradkettigen oder verzweigten Acyl-
 oder Alkoxy carbonyl-Rest mit jeweils bis zu 5 Kohlenstoffatomen oder einen geradkettigen oder verzweigten
 Alkyl-Rest mit bis zu 4 Kohlenstoffatomen dar, der gegebenenfalls mit einem Carboxy-, Hydroxyl-, Alkoxy carbonyl-Rest mit bis zu 5 Kohlenstoffatomen, einem Phenoxy- oder mit einem Benzoyl-Rest substituiert ist, oder sie stellen Fluor, Chlor, Brom, eine Nitro-, Trifluormethyl-Gruppe oder eine Gruppe der Formeln -OR⁵, -S(O)_a-R⁶, -(O-CH₂-CO)_b-NR⁷R⁸, -CO-NR⁹R¹⁰, -SO-NR¹¹R¹² oder -NH-SO₂-R¹³ dar,

15 worin gilt:

20 R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹ und R¹² sind gleich oder verschieden und bedeuten Wasserstoff, einen Cyclopropyl-, Cyclopentyl-, Cyclohexyl-, Chinolyl-, Pyridyl-, Imidazolyl-, 1,3-Thiazolyl- oder einen Thienyl-Rest, welche gegebenenfalls mit gleichen oder verschiedenen Substituenten aus der Reihe aus Fluor, Chlor, Brom, Jod, einer Cyano- oder aus einer Nitro-Gruppe oder mit einem geradkettigen oder verzweigten Alkyl-Rest mit bis zu 5 Kohlenstoffatomen substituiert sind,
 einen geradkettigen oder verzweigten Alkyl-, Alkenyl- oder einen Acyl-Rest mit jeweils bis zu 6 Kohlenstoffatomen,

25 oder

 sie bedeuten einen Phenyl-Rest, der gegebenenfalls mit gleichen oder verschiedenen Substituenten aus der Reihe aus einer Nitro-Gruppe, Fluor, Chlor, Brom, Jod, einem Carboxyl- oder aus einem geradkettigen oder verzweigten Alkoxy carbonyl-Rest mit bis zu 5 Kohlenstoffatomen mono- bis disubstituiert ist,
 oder

30 R⁵ bedeutet einen Benzyl-, Acetyl- oder einen Tetrahydropyran-Rest oder einen geradkettigen oder verzweigten Alkoxy carbonyl-Rest mit bis zu 4 Kohlenstoffatomen,
 einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 6 Kohlenstoffatomen, der mit einem Carboxyl-, Hydroxyl-, geradkettigen oder verzweigten Acyl- oder Alkoxy carbonyl-Rest mit jeweils bis zu 4 Kohlenstoffatomen, einem Phenoxy-, Benzoyl- oder mit einem Pyridyl-, Imidazolyl-, Thienyl- oder Furyl-Rest substituiert ist, welche gegebenenfalls mit Fluor, Chlor, Brom, einer Cyano-, Nitro-Gruppe oder mit einem geradkettigen oder verzweigten Alkyl-Rest mit bis zu 4 Kohlenstoffatomen substituiert sind,

35 oder

40 R⁵ bedeutet eine Gruppe der Formel -SO₂-R¹⁴,
 worin

45 R¹⁴ einen Phenyl-, Trifluormethyl- oder einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 3 Kohlenstoffatomen bedeutet,
 a bedeutet die Zahl 0, 1 oder 2,
 b bedeutet die Zahl 0 oder 1,
 R⁷ bedeutet Wasserstoff oder einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 3 Kohlenstoffatomen,
 R¹³ bedeutet einen Phenyl-, Trifluormethyl- oder einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 3 Kohlenstoffatomen,
50 R¹ stellt Wasserstoff, einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 4 Kohlenstoffatomen, einen t-Butoxy carbonyl-Rest oder eine Gruppe der Formel -CO-R¹⁵ dar,

 worin gilt:

55 R¹⁵ bedeutet eine Hydroxyl-Gruppe, einen geradkettigen oder verzweigten Alkoxy carbonyl-Rest mit bis zu 4 Kohlenstoffatomen, einen Cyclopentyl-, Cyclohexyl-, Pyridyl-, Pyrrolidinyl- oder einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 5 Kohlenstoffatomen, der gegebenenfalls mit Fluor, Chlor, Brom, einem Carboxyl- oder mit einem geradkettigen oder verzweigten Alkoxy carbonyl-Rest mit bis zu 4 Kohlenstoffatomen

substituiert ist, oder
einen Phenyl-Rest, der gegebenenfalls mit einem Hydroxy-, Carboxy- oder mit einem geradkettigen oder verzweigten Alkoxy- oder Alkoxycarbonyl-Rest mit jeweils bis zu 4 Kohlenstoffatomen substituiert ist,
L stellt ein Sauerstoff- oder Schwefelatom dar,
R² und R³ sind gleich oder verschieden und stellen Wasserstoff, einen Cyclobutyl-, Cyclopentyl-, Cyclohexyl- oder einen geradkettigen oder verzweigten Alkyl-, Alkoxy- oder Alkoxycarbonyl-Rest mit jeweils bis zu 6 Kohlenstoffatomen oder
einen Benzoyl- oder Phenyl-Rest dar, welche gegebenenfalls mit gleichen oder verschiedenen Substituenten aus der Reihe aus Fluor, Chlor, Brom, Jod, einer Carboxyl-, Cyano- oder aus einer Nitro-Gruppe oder mit einem geradkettigen oder verzweigten Alkyl-, Alkoxy- oder Alkoxycarbonyl-Rest mit jeweils bis zu 5 Kohlenstoffatomen mono- bis trisubstituiert sind,
oder
R² und R³ bilden zusammen mit dem Stickstoffatom einen Pyrrolidinyl-, Piperidinyl- oder einen Morpholinyl-Ring,
und
R⁴ stellt einen Phenyl-Rest dar, der gegebenenfalls mit gleichen oder verschiedenen Substituenten aus der Reihe aus einem Hydroxyl-, Thiophenyl-, Cyclopentyl-, Cyclohexyl-Rest, Fluor, Chlor, Brom, Jod, einer Nitro-Gruppe, einem Tetrazolyl-, Thiazolyl-, Furanyl-, Pyridyl-, Trifluormethyl-, Difluormethyl-, Cyano-, Carboxyl-, einem geradkettigen oder verzweigten Alkyl-, Alkoxy-, Alkoxycarbonyl- oder aus einem Acyl-Rest mit jeweils bis zu 6 Kohlenstoffatomen mono- bis trisubstituiert ist,
oder
der Phenyl-Rest ist gegebenenfalls mit einem Phenyl-Rest substituiert, der gegebenenfalls mit Fluor, Chlor oder Brom mono- bis disubstituiert ist, und Salze davon.

3. N-(3-Benzofuranyl)harnstoff-Derivate der Formel gemäß Anspruch 1,
worin gilt:

A und D sind gleich oder verschieden und stellen Wasserstoff, einen geradkettigen oder verzweigten Acyl- oder Alkoxycarbonyl-Rest mit jeweils bis zu 4 Kohlenstoffatomen oder einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 3 Kohlenstoffatomen dar, der gegebenenfalls mit einem Carboxyl- oder Alkoxycarbonyl-Rest mit bis zu 4 Kohlenstoffatomen, einem Phenoxy- oder Benzoyl-Rest substituiert ist, oder sie stellen Fluor, Chlor, Brom, eine Nitro-, Cyano-, Trifluormethyl-, Trifluormethoxy-Gruppe oder eine Gruppe der Formeln -OR⁵, -S(O)_aR⁶, -(O-CH₂-CO)_b-NR⁷R⁸, -CO-NR⁹R¹⁰, -SO₂NR¹¹R¹² oder -NH-SO₂R¹³ dar,
worin gilt:
R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹ und R¹² sind gleich oder verschieden und bedeuten Wasserstoff, einen Cyclopropyl-, Cyclopentyl-, Cyclohexyl-, Chinolyl-, Pyridyl-, Imidazolyl-, 1,3-Thiazolyl- oder einen Thienyl-Rest, welche gegebenenfalls mit gleichen oder verschiedenen Substituenten aus der Reihe aus Fluor, Chlor, Brom, Jod, einer Cyano- oder aus einer Nitro-Gruppe oder mit einem geradkettigen oder verzweigten Alkyl-Rest mit bis zu 3 Kohlenstoffatomen substituiert sind,
einen geradkettigen oder verzweigten Alkyl-, Alkenyl oder Acyl-Rest mit jeweils bis zu 3 Kohlenstoffatomen, oder
sie bedeuten einen Phenyl-Rest, der gegebenenfalls mit gleichen oder verschiedenen Substituenten aus der Reihe aus einer Nitro-Gruppe, Fluor, Chlor, Brom, Jod, einem Carboxyl- oder geradkettigen oder verzweigten Alkoxycarbonyl-Rest mit bis zu 3 Kohlenstoffatomen mono- bis disubstituiert ist,
oder
R⁵ bedeutet einen Benzyl-, Acetyl- oder Tetrahydropyranyl-Rest oder einen geradkettigen oder verzweigten Alkoxycarbonyl-Rest mit bis zu 3 Kohlenstoffatomen,
einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 4 Kohlenstoffatomen, der mit einem Carboxy-, Hydroxy-Rest, einem geradkettigen oder verzweigten Acyl- oder Alkoxycarbonyl-Rest mit jeweils bis zu 3 Kohlenstoffatomen, einem Phenoxy-, Benzoyl- oder mit einem Pyridyl-, Imidazolyl- oder Thienyl-Rest substituiert ist,
oder

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R⁵ bedeutet eine Gruppe der Formel -SO₂-R¹⁴,
worin

5 R¹⁴ einen Phenyl-, Trifluormethyl- oder einen Methyl-Rest bedeutet,
a bedeutet die Zahl 0, 1 oder 2,
b bedeutet die Zahl 0 oder 1,
R⁷ bedeutet Wasserstoff, einen Methyl- oder Ethyl-Rest,
R¹³ bedeutet einen Phenyl-, Trifluormethyl- oder einen Methyl-Rest,
10 R¹ stellt Wasserstoff oder einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 3 Kohlenstoffatomen
oder eine Gruppe der Formel -CO-R¹⁵ dar,

worin gilt:

15 R¹⁵ bedeutet eine Hydroxyl-Gruppe, einen geradkettigen oder verzweigten Alkoxy carbonyl-Rest mit bis zu 3 Kohlenstoffatomen, einen Cyclopentyl-, Cyclohexyl-, Pyridyl-, Pyrrolidinyl- oder einen geradkettigen oder verzweigten Alkyl-Rest mit bis zu 4 Kohlenstoffatomen, der gegebenenfalls mit Fluor, Chlor, Brom, einem Carboxyl- oder geradkettigen oder verzweigten Alkoxy carbonyl-Rest mit bis zu 3 Kohlenstoffatomen substituiert ist, oder

20 einen Phenyl-Rest, der gegebenenfalls mit einer Hydroxyl-Gruppe, einem Carboxyl- oder einem geradkettigen oder verzweigten Alkoxy- oder Alkoxy carbonyl-Rest mit jeweils bis zu 3 Kohlenstoffatomen substituiert ist, L stellt ein Sauerstoff- oder Schwefelatom dar,

25 R² und R³ sind gleich oder verschieden und stellen Wasserstoff, einen Cyclobutyl-, Cyclopentyl-, Cyclohexyl- oder einen geradkettigen oder verzweigten Alkyl-, Alkoxy carbonyl- oder Alkenyl-Rest mit jeweils bis zu 5 Kohlenstoffatomen oder einen Benzoyl- oder Phenyl-Rest dar, welche gegebenenfalls mit gleichen oder verschiedenen Substituenten aus der Reihe aus Fluor, Chlor, Brom, Jod, einer Carboxy-, Cyano- oder aus einer Nitro-Gruppe oder mit einem geradkettigen oder verzweigten Alkyl-, Alkoxy- oder Alkoxy carbonyl-Rest mit jeweils bis zu 3 Kohlenstoffatomen mono- bis trisubstituiert sind,

oder

30 R² und R³ bilden zusammen mit dem Stickstoffatom einen Pyrrolidinyl-Ring,
und

35 R⁴ stellt einen Phenyl-Rest dar, der gegebenenfalls mit gleichen oder verschiedenen Substituenten aus der Reihe aus einem Hydroxyl-, Thiophenyl-, Cyclopentyl-, Cyclohexyl-Rest, Fluor, Chlor, Brom, einer Nitro-Gruppe, einem Tetrazolyl-, Thiazolyl-, Furanyl-, Pyridyl-, Trifluormethyl-, Difluormethyl-, Cyano-, Carboxyl-, aus einem geradkettigen oder verzweigten Alkyl-, Alkoxy-, Alkoxy carbonyl- oder Acyl-Rest mit jeweils bis zu 5 Kohlenstoffatomen mono- bis trisubstituiert ist, oder

40 der Phenyl-Rest ist gegebenenfalls mit einem Phenyl-Rest substituiert, der gegebenenfalls mit Chlor mono- bis disubstituiert ist,

und Salze davon.

4. Die Verbindung der Formel

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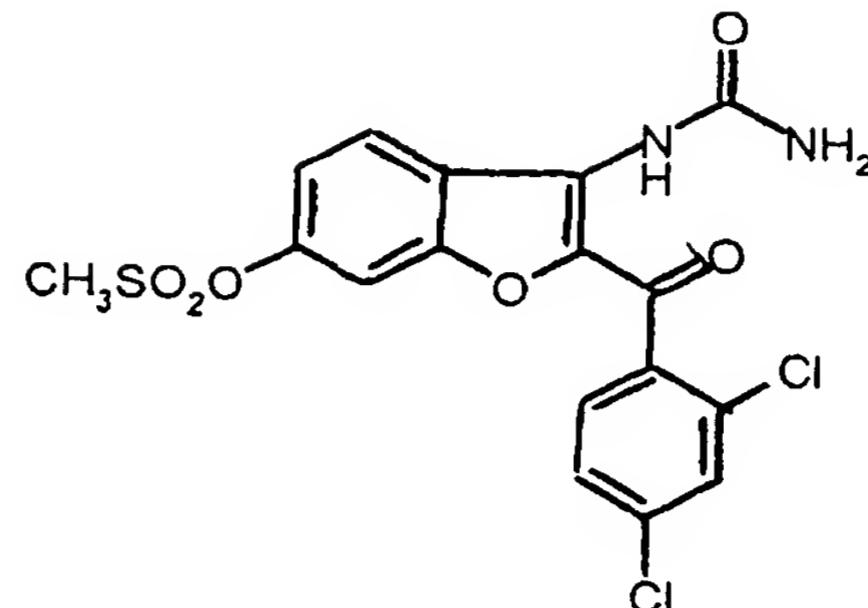
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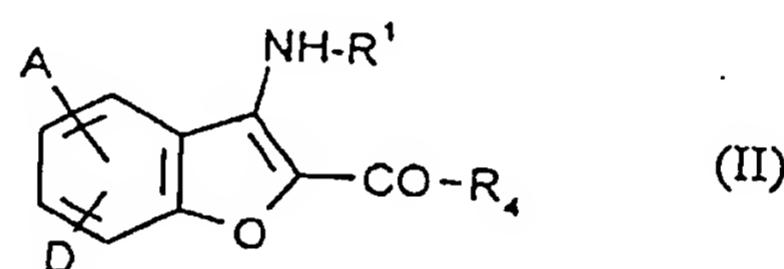


gemäß Anspruch 1.

20 5. N-(3-Benzofuranyl)harnstoff-Derivate gemäß einem der Ansprüche 1 bis 4 zur therapeutischen Verwendung.
 6. Verfahren zur Herstellung von N-(3-Benzofuranyl)harnstoff-Derivaten gemäß einem der Ansprüche 1 bis 4,
 dadurch gekennzeichnet, daß Verbindungen der allgemeinen Formel (II):

25

30



worin

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A, D, R¹ und R⁴ die oben angegebenen Bedeutungen haben,
 mit Verbindungen der allgemeinen Formel (III):

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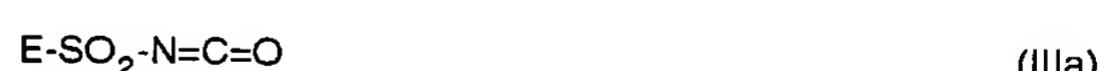


worin

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L und R² die oben angegebenen Bedeutungen haben, in inerten Lösungsmitteln, gegebenenfalls in der Gegenwart einer Base und/oder in der Gegenwart eines Hilfsstoffs, zur Reaktion gebracht werden,
 und daß im Fall von R²/R³ = H und L = O
 Verbindungen der allgemeinen Formel (II) mit
 Verbindungen der allgemeinen Formel (IIIa):

50



worin

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E Halogen, vorzugsweise Chlor, bedeutet, zur Reaktion gebracht werden,
 und daß im Fall von R²/R³ = H und L = S
 Verbindungen der allgemeinen Formel (II) mit NH_4SCN zur Reaktion gebracht werden,

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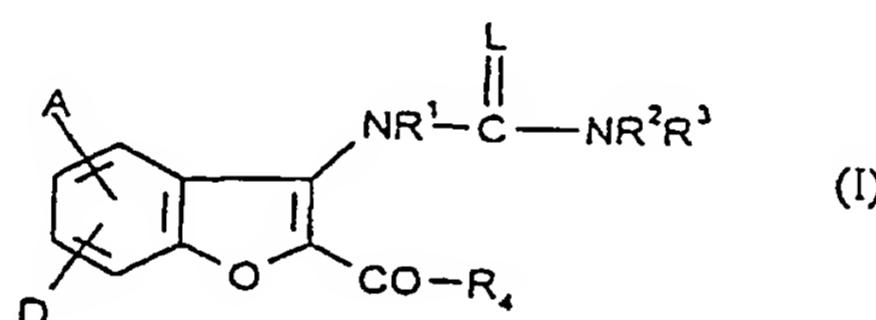
und daß im Fall von R¹, R² und/oder R³ ≠ H die Amino-Gruppen gegebenenfalls mit üblichen Verfahren derivatisiert werden.

- 5 7. Zusammensetzung, enthaltend mindestens ein N-(3-Benzofuranyl)harnstoff-Derivat gemäß einem der Ansprüche 1 bis 4 und ein pharmakologisch geeignetes Verdünnungsmittel.
- 10 8. Zusammensetzung gemäß Anspruch 7 zur Behandlung akuter und chronischer Entzündungskrankheiten.
- 15 9. Verfahren zur Herstellung von Zusammensetzungen gemäß Anspruch 7 oder 8, dadurch gekennzeichnet, daß das N-(3-Benzofuranyl)harnstoff-Derivat zusammen mit üblichen Hilfsstoffen in eine geeignete Anwendungsform gebracht wird.
- 20 10. Verwendung von N-(3-Benzofuranyl)harnstoff-Derivaten gemäß einem der Ansprüche 1 bis 4 zur Herstellung von Medikamenten.
- 25 11. Verwendung gemäß Anspruch 10 zur Herstellung von Medikamenten zur Behandlung akuter und chronischer Entzündungskrankheiten.

Revendications

1. Dérivés de la N-(3-benzofuranyl)urée répondant à la formule générale (I)

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dans laquelle

40 A et D sont identiques ou différents et représentent un atome d'hydrogène, un groupe acyle ou un groupe alcoxycarbonyle à chaînes droites ou ramifiées contenant respectivement jusqu'à 6 atomes de carbone, ou encore un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 6 atomes de carbone, qui peut porter le cas échéant un ou plusieurs substituants carboxyle ou alcoxycarbonyle identiques ou différents contenant jusqu'à 6 atomes de carbone, phénoxy ou benzoyle, ou représentent un atome d'halogène, un groupe carboxyle, un groupe cyano, un groupe nitro, un groupe trifluorométhyle, un groupe trifluorométhoxy ou encore un groupe répondant aux formules -OR⁵, -S(O)_aR⁶, -(O-CH₂-CO)_b-NR⁷R⁸, -CO-NR⁹R¹⁰, -SO₂-NR¹¹R¹² ou -NH-SO₂R¹³, dans lesquelles

45 R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹ et R¹²

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sont identiques ou différents et représentent un atome d'hydrogène, un groupe cycloalkyle contenant de 3 à 6 atomes de carbone, un groupe benzyle ou encore un radical hétérocyclique penta- à heptagonal, saturé ou insaturé, contenant jusqu'à 3 atomes de carbone, choisi parmi la série comprenant N, S et O et auquel un noyau phényle peut être condensé, et qui le cas échéant porte un ou plusieurs substituants identiques ou différents choisis parmi la série comprenant des substituants halogéno, cyano, nitro ou encore alkyle à chaînes droites ou ramifiées contenant jusqu'à 6 atomes de carbone, ou

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représentent un groupe alkyle, un groupe alcényle ou un groupe acyle contenant respectivement jusqu'à 8 atomes de carbone, ou

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ou

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R^5 représente un groupe protecteur du groupe hydroxyle ou un groupe alcoxycarbonyle à chaîne droite ou ramifiée contenant jusqu'à 6 atomes de carbone, ou
 représente un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 8 atomes de carbone, qui porte à titre de substituants identiques ou différents, un ou plusieurs groupes carboxyle, hydroxyle, acyle ou alcoxycarbonyle à chaînes droites ou ramifiées contenant respectivement jusqu'à 6 atomes de carbone, phénoxy, benzoyle ou encore un radical hétérocyclique insaturé pentagonal à heptagonal contenant jusqu'à 3 hétéroatomes choisis parmi la série comprenant N, S et/ou O, qui porte le cas échéant un ou plusieurs substituants identiques ou différents halogéno, cyano, nitro ou alkyle à chaînes droites ou ramifiées contenant jusqu'à 6 atomes de carbone,

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ou

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R^5 représente un groupe répondant à la formule SO_2R^{14} dans laquelle

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R^{14} représente un groupe phényle, un groupe trifluorométhyle ou un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 4 atomes de carbone,

a représente le nombre 0, 1 ou 2,

b représente le nombre 0 ou 1,

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R^7 représente un atome d'hydrogène ou un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 4 atomes de carbone,

R^{13} représente un groupe aryle contenant jusqu'à 6 à 10 atomes de carbone, un groupe trifluorométhyle ou un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 6 atomes de carbone,

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R^1 représente un atome d'hydrogène, un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 6 atomes de carbone, un groupe protecteur du groupe amino ou un groupe répondant à la formule -CO-R¹⁵ dans laquelle

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R^{15} représente un groupe hydroxyle, un groupe alcoxycarbonyle à chaîne droite ou ramifiée contenant jusqu'à 6 atomes de carbone, un groupe cycloalkyle contenant jusqu'à 3 à 6 atomes de carbone, un groupe pyridyle, un groupe pyrrolidinyle ou un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 8 atomes de carbone, qui porte le cas échéant un ou plusieurs substituants identiques ou différents halogéno, carboxyle ou alcoxycarbonyle à chaînes droites ou ramifiées contenant jusqu'à 6 atomes de carbone, ou représente un groupe phényle qui porte le cas échéant un ou plusieurs substituants identiques ou différents hydroxyle, carboxyle ou encore alcoxy ou alcoxycarbonyle à chaînes droites ou ramifiées contenant respectivement jusqu'à 6 atomes de carbone,

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L représente un atome d'oxygène ou un atome de soufre,

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R^2 et R^3 sont identiques ou différents et représentent

un atome d'hydrogène, un groupe cycloalkyle contenant jusqu'à 6 atomes de carbone, un groupe alkyle, un groupe alcoxycarbonyle ou un groupe alcényle à chaînes droites ou ramifiées contenant respectivement jusqu'à 8 atomes de carbone, ou représentent un groupe benzoyle ou un groupe aryle

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contenant de 6 à 10 atomes de carbone, qui portent le cas échéant de un à trois substituants identiques ou différents choisis parmi la série comprenant des substituants halogéno, cyano, nitro, carboxyle, alkyle, alcoxy, alcoxycarbonyle ou acyle à chaînes droites ou ramifiées, contenant respectivement jusqu'à 6 atomes de carbone,

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ou

R² et R³ forment ensemble avec l'atome d'azote un composé hétérocyclique saturé penta- à heptagonal contenant le cas échéant un atome d'oxygène supplémentaire,

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et

R⁴ représente un groupe phényle qui porte le cas échéant de un à trois substituants identiques ou différents choisis parmi la série comprenant des substituants hydroxyle, thiophényle, cycloalkyle contenant jusqu'à 3 à 6 atomes de carbone, halogéno, nitro, tétrazolyde, thiazolyde, furanyle, pyridyle, trifluorométhyle, difluorométhyle, cyano, carboxyle, alkyle, alcoxy, alcoxycarbonyle ou acyle à chaînes droites ou ramifiées, contenant respectivement jusqu'à 8 atomes de carbone,
ou bien le groupe phényle est, le cas échéant, substitué par un groupe phényle lequel est, le cas échéant, mono- à disubstitué par un atome d'halogène ou par un groupe répondant aux formules -NR¹⁶R¹⁷, -SR¹⁸, -SO₂R¹⁹ ou -O-SO₂R²⁰,
dans lesquelles

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R¹⁶ et R¹⁷ ont la signification mentionnée ci-dessus pour R⁷ et R⁸ et sont identiques ou différents de ces derniers,

ou

R¹⁶ représente un atome d'hydrogène,

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et

R¹⁷ représente un groupe acyle à chaîne droite ou ramifiée contenant jusqu'à 6 atomes de carbone,

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R¹⁸ représente un atome d'hydrogène ou un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 6 atomes de carbone,

R¹⁹ et R²⁰ sont identiques ou différents et représentent un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 6 atomes de carbone, un groupe benzyle ou un groupe phényle,

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ainsi que leurs sels.

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2. Dérivés de la N-(3-benzofuranyl)urée répondant à la formule selon la revendication 1, dans laquelle

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A et D sont identiques ou différents et représentent un atome d'hydrogène, un groupe acyle ou un groupe alcoxycarbonyle à chaînes droites ou ramifiées contenant respectivement jusqu'à 5 atomes de carbone, ou encore un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 4 atomes de carbone, qui peut porter le cas échéant un ou plusieurs substituants carboxyle, hydroxyle ou alcoxycarbonyle identiques ou différents contenant jusqu'à 5 atomes de carbone, phénoxy ou benzoyle, ou représentent un atome de fluor, un atome de chlore, un atome de brome, un groupe nitro, un groupe trifluorométhyle ou encore un groupe répondant aux formules -OR⁵, -S(O)_aR⁶, -(O-CH₂-CO)_b-NR⁷R⁸, -CO-NR⁹R¹⁰, -SO₂-NR¹¹R¹² ou -NH-SO₂R¹³, dans lesquelles

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R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹ et R¹²

sont identiques ou différents et représentent un atome d'hydrogène, un groupe cyclopropyle, un groupe cyclopentyle, un groupe cyclohexyle, un groupe quinolyle, un groupe pyridyle, un groupe imidazolyde, un groupe 1,3-thiazolyde ou un groupe thiényle, qui portent le cas échéant un ou plusieurs substi-

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tuants identiques ou différents choisis parmi la série comprenant des substituants fluoro, chloro, bromo, iodo, cyano, nitro ou encore alkyle à chaînes droites ou ramifiées contenant jusqu'à 5 atomes de carbone, représentent un groupe alkyle, un groupe alcényle ou un groupe acyle à chaînes droites ou ramifiées contenant respectivement jusqu'à 6 atomes de carbone, ou représentent un groupe phényle qui porte le cas échéant de un à deux substituants identiques ou différents choisis parmi la série comprenant des substituants nitro, fluoro, chloro, bromo, iodo, carboxyle ou alcoxycarbonyle à chaînes droites ou ramifiées contenant jusqu'à 5 atomes de carbone.

ou

	R ⁵	représente un groupe benzyle, un groupe acétyle ou un groupe tétrahydropyranyle ou encore un groupe alcoxycarbonyle à chaîne droite ou ramifiée contenant jusqu'à 4 atomes de carbone, ou représente un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 6 atomes de carbone, qui porte un ou plusieurs substituants identiques ou différents carboxyle, hydroxyle, acyle ou alcoxycarbonyle à chaînes droites ou ramifiées contenant respectivement jusqu'à 4 atomes de carbone, phenoxy, benzoyle ou encore pyridyle, imidazolyde, thiényle ou furyle, qui portent le cas échéant un ou plusieurs substituants identiques ou différents fluoro, chloro, bromo, cyano, nitro ou alkyle à chaînes droites ou ramifiées contenant jusqu'à 4 atomes de carbone,
20		ou
25	R ⁵	représente un groupe répondant à la formule -SO ₂ -R ¹⁴ dans laquelle
30	R ¹⁴	représente un groupe phényle, un groupe trifluorométhyle ou un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 3 atomes de carbone,
35	a	représente le nombre 0, 1 ou 2,
	b	représente le nombre 0 ou 1,
	R ⁷	représente un atome d'hydrogène ou un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 3 atomes de carbone,
	R ¹³	représente un groupe phényle, un groupe trifluorométhyle ou un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 3 atomes de carbone,
40	R ¹	représente un atome d'hydrogène, un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 4 atomes de carbone, un groupe tert.-butoxycarbonyle ou un groupe répondant à la formule -CO-R ¹⁵ dans laquelle
45	R ¹⁵	représente un groupe hydroxyle, un groupe alcoxycarbonyle à chaîne droite ou ramifiée contenant jusqu'à 4 atomes de carbone, un groupe cyclopentyle, un groupe cyclohexyle, un groupe pyridyle, un groupe pyrrolidinyle ou encore un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 5 atomes de carbone, qui porte le cas échéant un ou plusieurs substituants identiques ou différents fluoro, chloro, bromo, carboxyle ou alcoxycarbonyle à chaînes droites ou ramifiées contenant jusqu'à 4 atomes de carbone, ou représente un groupe phényle qui porte le cas échéant un ou plusieurs substituants identiques ou différents hydroxyle, carboxyle ou encore alcoxy ou alcoxycarbonyle à chaînes droites ou ramifiées contenant respectivement jusqu'à 4 atomes de carbone,
50	L	représente un atome d'oxygène ou un atome de soufre,
55	R ² et R ³	sont identiques ou différents et représentent un atome d'hydrogène, un groupe cyclobutyle, un groupe cyclopentyle, un groupe cyclohexyle ou un groupe alkyle, un groupe alcoxycarbonyle

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ou un groupe alcényle à chaînes droites ou ramifiées, contenant respectivement jusqu'à 6 atomes de carbone, ou
5 représentent un groupe benzoyle ou un groupe phényle qui portent le cas échéant de un à trois substituants identiques ou différents choisis parmi la série comprenant des substituants fluoro, chloro, bromo, iodo, carboxyle, cyano, nitro ou encore alkyle, alcoxy ou alcoxycarbonyle à chaînes droites ou ramifiées contenant respectivement jusqu'à 5 atomes de carbone,

ou

10 R² et R³ forment ensemble avec l'atome d'azote un noyau pyrrolidinyle, un noyau pipéridinyle ou un noyau morpholinyle,

et

15 R⁴ représente un groupe phényle qui porte le cas échéant de un à trois substituants identiques ou différents choisis parmi la série comprenant des substituants hydroxyle, thiophényle, cyclopentyle, cyclohexyle, fluoro, chloro, bromo, iodo, nitro, tétrazolyde, thiazolyde, furanyle, pyridyle, trifluorométhyle, difluorométhyle, cyano, carboxyle, alkyle, alcoxy, alcoxycarbonyle ou acyle à chaînes droites ou ramifiées, contenant respectivement jusqu'à 6 atomes de carbone, ou bien le groupe phényle est, le cas échéant, substitué par un groupe phényle 20 lequel est, le cas échéant, mono- à disubstitué par un atome de fluor, par un atome de chlore ou par un atome de brome,

ainsi que leurs sels.

25 3. Dérivés de la N-(3-benzofuranyl)urée répondant à la formule selon la revendication 1, dans laquelle

A et D sont identiques ou différents et représentent un atome d'hydrogène, un groupe acyle ou un groupe 30 alcoxycarbonyle à chaînes droites ou ramifiées contenant respectivement jusqu'à 4 atomes de carbone, ou encore un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 3 atomes de carbone, qui peut porter le cas échéant un ou plusieurs substituants carboxyle ou alcoxycarbonyle identiques ou différents contenant jusqu'à 4 atomes de carbone, phénoxy ou benzoyle,

35 ou représentent un atome de fluor, un atome de chlore, un atome de brome, un groupe nitro, un groupe cyano, un groupe trifluorométhyle, un groupe trifluorométhoxy ou un groupe répondant aux formules -OR⁵, -S(O)_aR⁶, -(O-CH₂-CO)_b-NR⁷R⁸, -CO-NR⁹R¹⁰, -SO₂-NR¹¹R¹² ou -NH-SO₂R¹³, dans lesquelles

40 R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹ et R¹² sont identiques et représentent un atome d'hydrogène, un groupe cyclopropyle, un groupe cyclopentyle, un groupe cyclohexyle, un groupe quinolyle, un groupe pyridyle, un groupe imidazolyde, un groupe 1,3-thiazolyde ou un groupe thiényle, qui portent le cas échéant un ou plusieurs substituants identiques ou différents choisis parmi la série comprenant des substituants fluoro, chloro, bromo, iodo, cyano, nitro ou encore alkyle à chaînes droites ou ramifiées contenant jusqu'à 3 atomes de carbone,

45 représentent un groupe alkyle, un groupe alcényle ou un groupe acyle à chaînes droites ou ramifiées contenant respectivement jusqu'à 3 atomes de carbone, ou représentent un groupe phényle qui porte le cas échéant de un à deux substituants identiques ou différents choisis parmi la série comprenant des substituants nitro, fluoro, chloro, bromo, iodo, carboxyle ou alcoxycarbonyle à chaînes droites ou ramifiées contenant jusqu'à 3 atomes de carbone,

50 ou

55 R⁵ représente un groupe benzyle, un groupe acétyle ou un groupe tétrahydropyranyle ou encore

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un groupe alcoxycarbonyle à chaîne droite ou ramifiée contenant jusqu'à 3 atomes de carbone,
ou
représente un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 4 atomes de carbone,
qui porte un ou plusieurs substituants identiques ou différents carboxyle, hydroxyle, acyle ou
alcoxycarbonyle à chaînes droites ou ramifiées contenant respectivement jusqu'à 3 atomes de
carbone, phénoxy, benzoyle ou encore pyridyle, imidazolyde ou thiényle,

ou

10 R⁵ représente un groupe répondant à la formule -SO₂-R¹⁴
dans laquelle

R¹⁴ représente un groupe phényle, un groupe trifluorométhyle ou un groupe méthyle,

15 a représente le nombre 0, 1 ou 2,
b représente le nombre 0 ou 1,

20 R⁷ représente un atome d'hydrogène, un groupe méthyle ou un groupe éthyle,

R¹³ représente un groupe phényle, un groupe trifluorométhyle ou un groupe méthyle,

25 R¹ représente un atome d'hydrogène ou un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 3 atomes
de carbone ou encore un groupe répondant à la formule -CO-R¹⁵
dans laquelle

30 R¹⁵ représente un groupe hydroxyle, un groupe alcoxycarbonyle à chaîne droite ou ramifiée contenant
jusqu'à 3 atomes de carbone, un groupe cyclopentyle, un groupe cyclohexyle, un groupe pyridyle, un
groupe pyrrolidinyle ou encore un groupe alkyle à chaîne droite ou ramifiée contenant jusqu'à 4 atomes
de carbone, qui porte le cas échéant un ou plusieurs substituants identiques ou différents fluoro,
chloro, bromo, carboxyle ou alcoxycarbonyle à chaînes droites ou ramifiées contenant jusqu'à 3 ato-
mes de carbone, ou
représente un groupe phényle qui porte le cas échéant un ou plusieurs substituants identiques ou
différents hydroxyle, carboxyle ou encore alkoxy ou alcoxycarbonyle à chaînes droites ou ramifiées
contenant respectivement jusqu'à 3 atomes de carbone,

35 L représente un atome d'oxygène ou un atome de soufre,

40 R² et R³ sont identiques ou différents et représentent un atome d'hydrogène, un groupe cyclobutyle, un groupe
cyclopentyle, un groupe cyclohexyle ou encore un groupe alkyle, un groupe alcoxycarbonyle ou un
groupe alcényle à chaînes droites ou ramifiées contenant respectivement jusqu'à 5 atomes de car-
bone, ou
représentent un groupe benzoyle ou un groupe phényle qui portent le cas échéant de un à trois subs-
tituants identiques ou différents choisis parmi la série comprenant des substituants fluoro, chloro,
bromo, iodo, carboxyle, cyano, nitro ou encore alkyle, alkoxy ou alcoxycarbonyle à chaînes droites
ou ramifiées contenant respectivement jusqu'à 3 atomes de carbone,

45 ou

50 R² et R³ forment ensemble avec l'atome d'azote un noyau pyrrolidinyle,
et

55 R⁴ représente un groupe phényle qui porte le cas échéant de un à trois substituants identiques ou différents
choisis parmi la série comprenant des substituants hydroxyle, thiophényle, cyclopentyle, cyclohexyle, fluoro,
chloro, bromo, nitro, tétrazolyle, thiazolyle, furanyle, pyridyle, trifluorométhyle, difluorométhyle, cyano, car-
boxyle, alkyle, alkoxy, alcoxycarbonyle ou acyle à chaînes droites ou ramifiées contenant respectivement
jusqu'à 5 atomes de carbone, ou bien le groupe phényle est, le cas échéant, substitué par un groupe phényle

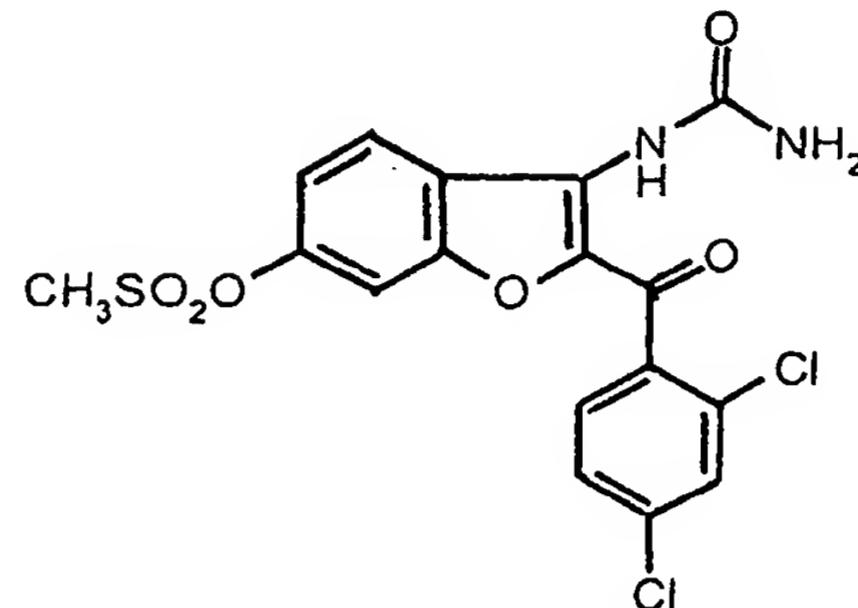
lequel est, le cas échéant, mono- à disubstitué par un atome de chlore,
ainsi que leurs sels.

5 4. Dérivé répondant à la formule

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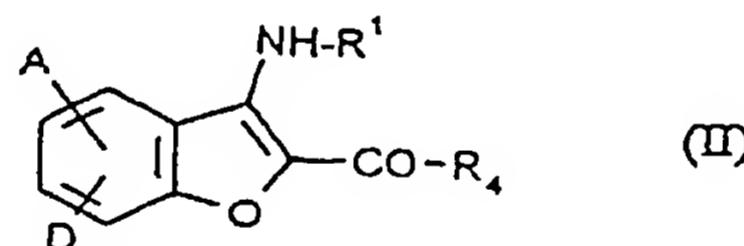


selon la revendication 1.

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- 5. Dérivés de la N-(3-benzofuranyl)urée selon les revendications 1 à 4 pour une utilisation thérapeutique.
- 6. Procédé pour la préparation de dérivés de la N-(3-benzofuranyl)urée selon les revendications 1 à 4 , caractérisé en ce qu'on fait réagir
30 des composés répondant à la formule générale (II)

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dans laquelle

A, D, R¹ et R⁴ ont la signification susmentionnée, avec des composés répondant à la formule générale (III)

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dans laquelle

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L et R² ont la signification susmentionnée,
dans des solvants inertes, si cela s'avère approprié en présence d'une base et/ou en présence d'un
adjuvant,
et dans le cas où R²/R³ = H et L = O, on fait réagir des composés répondant à la formule générale (II)
avec des composés répondant à la formule générale (IIIa)

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et dans le cas où $R^2/R^3 = H$ et $L = S$,
on fait réagir des composés répondant à la formule générale (II) avec NH_4SCN ,
et dans le cas où R^1, R^2 et/ou $R^3 \neq H$, on dérive les groupes amino le cas échéant via des procédés courants.

5 7. Composition contenant au moins un dérivé de la N-(3-benzofuranyl)urée selon les revendications 1 à 4 et un diluant pharmacologiquement acceptable.

10 8. Composition selon la revendication 7 pour le traitement de processus inflammatoires aigus et chroniques.

9. Procédé pour la préparation de compositions selon les revendications 7 et 8 caractérisé en ce qu'on amène dans une forme d'application appropriée, le dérivé de la N-(3-benzofuranyl)urée conjointement avec des adjuvants habituels.

15 10. Utilisation de dérivés de la N-(3-benzofuranyl)urée selon les revendications 1 à 4 pour la préparation de médicaments.

11. Utilisation selon la revendication 10 pour la préparation de médicaments destinés au traitement de processus inflammatoires aigus et chroniques.

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